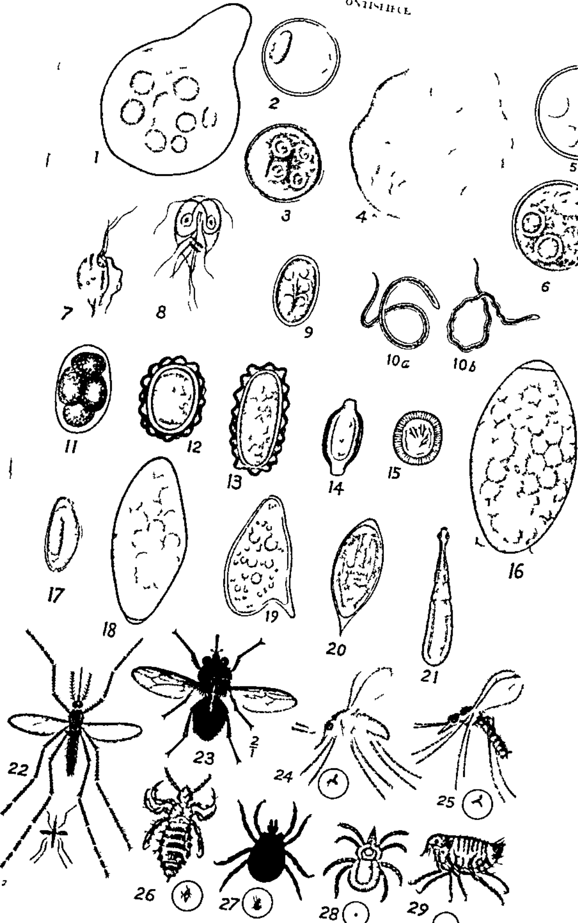

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Frontispiece A

1	*Entamœba histolytica*	} × 1,000	
2	*Entamœba histolytica* cyst, in saline		
3	*Entamœba histolytica* cyst; iodine stained.		
4	*Entamœba coli.*		
5	*Entamœba coli* cyst; in saline		
6	*Entamœba coli* 4-nucleated cyst iodine stained		
7	*Trichomonas hominis*		
8	Giardia		
9	Giardia cyst		
10a	Microfilaria of *Wuchereria bancrofti*	} × 350	
10b	Microfilaria of *Wuchereria malayi*		
11	Hookworm ova		
12	Ascaris ova (fertilized)		
13	Ascaris ova (unfertilized)		
14	*Trichuris trichiura* (*Trichocephalus trichiurus*)		
15	*Tænia saginata*		
16	*Fasciolopsis buskii*		

17	*Enterobius vermicularis* × 350	
18	*Gastrodiscoides hominis* × 275	
19	*Schistosoma mansoni* × 200	
20	*Schistosoma hæmatobium* × 200	
21	Echinococcus × 7	
22	*Aedes ægypti* × 5	
23	*Glossina palpalis* × 2	
24	*Phlebotomus papatasii*	} × 6
25	*Phlebotomus argentipes*	
26	*Pediculus humanus* × 8	
27	*Dermacentor andersoni* × 6	
28	*Trombicula akamushi* adult × 8 (Nymph inset)	
29	*Xenopsylla cheopis* × 8.	
	(Actual size of insects inset in ring)	

The approximate magnification of each figure is shown

Frontispiece B

(Giemsa's stain · × 2,000)

A Benign tertian (*Plasmodium vivax*)

Young ring form, amœboid trophozoite, three-quarter-grown trophozoite, developing schizont, dividing schizont, male gametocyte, and female gametocyte

B Malignant tertian (*P falciparum*)

Young ring form, four ring forms, including one accolé form, in one red cell, band form, a larger ring form with Maurer's dots, mature schizont, or *rosette, male crescent, and female crescent*

C Quartan (*P malariæ*)

Young ring form, young band form, large band form, schizont, merozoites (free), male gametocyte, and female gametocyte

D (*P ovale*)

Young ring form, band form, two schizonts in one corpuscle, infected corpuscle showing a fimbriated outline, dividing schizont, male gametocyte; and female gametocyte

E Trypanosomes

(*a*) *T gambiense* (*b*) *T brucei* (*c*) *T cruzi*.

F Bartonella

G *Spirillum minus*

H *Treponema recurrentis*

I Leishmania

(*a*) 'Round' forms (Leishman Donovan bodies) from spleen puncture

(*b*) 'Torpedo' forms of Leishman Donovan bodies

(*c*) The flagellate forms

J *Leptospira icterohæmorrhagiæ* (the rope-like spirals would not show in a Giemsa-stained specimen)

K Comma bacilli

THE

PRINCIPLES AND PRACTICE

OF

TROPICAL MEDICINE

BY

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LITHOGRAPHED IN THE UNITED STATES OF AMERICA

PREFACE

The writer has attempted to give an accurate and concise account of the more important tropical diseases from the points of view of epidemiology

ment

as me

anæmia in the tropics and snakes and snake bite He hopes that the book will be useful to the student the practitioner and the public health worker and that it will be looked upon rather as a textbook than as a book of reference For this reason he has not attempted to follow that mirage completeness either as regards the individual subjects or the field of

g the presenta

ited to exercise

ppear to him to

uestion that is discussed in the text of this book (*see* p 3) No very satisfactory answer is given However the writer still had to decide what he was to include in the book and although he followed a preconceived plan he admits that many of his decisions are impossible to defend on logical grounds and that some are difficult to uphold on any grounds

Perhaps the most glaring omissions are two infectious diseases which are of very great importance in the tropics namely smallpox and typhoid fever These diseases are of course not confined to the tropics—but this is true of many other diseases included in the book—nor do they present any very special features in the tropics It is true that the mild form of smallpox alastrim occurs in many tropical countries and provides a degree of protection to the population against infection by the more virulent strains of the virus This form of the disease has seldom been recognized in India where in some recent years there have been nearly a hundred thou and smallpox deaths annually despite the extensive vaccination organization

The immunity to typhoid fever reputed to be enjoyed by some native populations in the tropics is almost certainly a result of infection in child hood With the advance of sanitation in India for example paradoxi cally the disease appears to be increasing especially in the adolescent and young adult groups of the middle class indigenous population This ap parent increase is probably the result of a higher rate of infection in the economically more important age groups Typhoid is however in the writer s experience generally a milder disease in the tropics

Both these diseases are well described in the ordinary textbooks of

omission is justified

ily excused In many tropical

bid to oust malaria from its

th and sickness and although

tuberculosis is a cosmopolitan disease its epidemiology pathology and symptomatology certainly exhibit special features when it occurs in tropical populations The only excuse the writer can offer is that our present state

of knowledge of tuberculosis in the tropics is not sufficiently standardized to make possible the preparation of a concise account of the subject, and he therefore felt that it would be better to omit it altogether

Another obvious omission is a discussion on eye diseases and blindness in the tropics This is a very important subject in which most practitioners in the tropics will sooner or later find themselves involved, but it is a specialist subject that appears to demand separate treatment

In most books on tropical medicine considerable space is devoted to mycotic infections, sometimes—the writer feels—more than can logically be justified, although he himself has possibly erred too far in the other direction by omitting all reference to the systemic mycoses and only including those of the superficial mycoses that are common and particularly troublesome in the tropics

Turning to errors of commission, one finds it difficult to justify the inclusion of tularæmia which is in no sense a tropical disease, though its modes of transmission are similar to those of several tropical diseases, it is however the usual practice to include tularæmia in books on tropical medicine and the writer has, perhaps somewhat weakly, fallen into line Simi-

[illegible] not tropical,

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laboratory work on a more extensive scale will require a laboratory handbook, such as Craig's *Laboratory Diagnosis of Protozoan Diseases* or the more comprehensive *Laboratory Methods of the United States Army* by Simmons and Gentzkow

LITERATURE

The writer would have been failing in his duty, if in writing this book he had not made free use of the existing textbooks of tropical medicine, especially Rogers and Megaw's *Tropical Medicine*, Manson Bahr's *Manson's Tropical Diseases*, Strong's *Stitt's Tropical Medicine*, and Craig and Faust's *Clinical Parasitology* Scott's *History of Tropical Medicine* and the appropriate chapters in the *British Encyclopædia of Medical Practice* were also used freely As for the periodicals, the special journals, the *American Journal of Tropical Medicine*, the *Transactions of the Royal Society of Tropical Medicine*, the *Annals of Tropical Medicine and Para-* [illegible] the Indian jour- [illegible] *Medical Research*, [illegible] the *Journal of* [illegible] ourse, above all, the comprehensive *Tropi-* [illegible] led the most useful material

REFERENCES

[illegible] book

workers freely by name without giving any supporting textual re This, the present writer has found a little irritating, and so he has the practice of referring to individual workers by name, perhaps l quently, but as far as possible giving the specific reference when h mention a name Repetition has been avoided as far as possible, s when a reference is missing the reader should turn to an earlier chap a cognate subject A few classical references are included, but for the part the references are to recent work This rather haphazard selectio references has led, the writer finds in retrospect, to his giving promin to his own work, and to some extent to that of his immediate associ out of all proportion to their importance, and to his frequently failing mention the more important work of others, which he hopes will be forgiv

Such references as are given the writer believes are accurate F checking the references in the earlier chapters, he has to thank Mr Sur, t librarian of the Calcutta School of Tropical Medicine

ILLUSTRATIONS

The majority of the figures and illustrations are original When they have been borrowed from the books or papers of other writers the source is given Permission to use these illustrations is gratefully acknowledged The one or two exceptions to this rule are charts that have been taken from the museum of the Calcutta School of Tropical Medicine It has not been possible to trace their source The original drawings of the coloured plates were made by Mr H Roy, the artist at the Calcutta School, Mr Roy, Mr Mullick (the assistant artist at the Calcutta School), Mrs Lawrence, and Miss Vera Morel the two latter of New Orleans drew the 'cycles' from the writer's very crude sketches The assistance given by these artists is gratefully acknowledged

The writer has to thank Colonel W S Robertson commanding the 47th British General Hospital, for the loan of the skiagrams shown in Plates XIII and XIV and for the temperature charts from which Fig 135 was copied

ACKNOWLEDGMENTS

The writer's sincerest thanks are due to Lieut -Colonel Seward, Officer in charge, Medical Division, 47th British General Hospital, for reading through all the proofs of the earlier chapters, for pointing out many mistakes that had been overlooked and for making several valuable sugges[t]ions that have now been adopted, to Dr R N Chaudhuri for material [h]elp in several chapters and assistance with the proof reading, to Dr Harry [..]enekje for his useful note on bejel, to Dr Sundara Rao for his collabo[ra]tion in the chapter on guinea-worm and for his assistance with the chap[ter] on filariasis, especially for the photographs illustrating that chapter Dr S K Ganguli for his collaboration in the chapter on snakes and [sna]ke-bite, and above all to Dr John Lowe not only for his contribution, [the] chapter on leprosy, but for reading through the typescript and proofs [th]e first part of the book and making many constructive criticisms

Valuable assistance has been given by many of the writer's colleagues [Ca]lcutta* and at Tulane His thanks are especially due to Dr Grace [..]mith, Associate Professor of Medicine, Tulane Medical School, for

[*T]he first part of this book up to and including the chapter on leprosy was pub[lished p]rivately in India in 1943 The completed book is now published in the United [..] It has been possible to make a certain number of corrections alterations [..] in the previously published part of the book to conform with re[..] [v]arious reasons these have had to be strictly limited

constructive criticism in the chapters on diet and dietetic diseases to Dr F H Wilson Associate Professor of Parasitology for reading the typescript of most of the later chapters especially those on helminthic infections and for pointing out many mistakes and inaccuracies to his friend Dr J Walker Associate Professor of Tropical Medicine for his caustic but usually helpful criticism especially in the chapters on malaria sleeping sickness and yaws to Miss A M Lyman for her careful reading of the typescript and to his secretary Mrs Virginia Gill for her accurate typing

The section of helminthic diseases was written in the helminthological atmosphere of the Department of Tropical Medicine of the Tulane Medical School where the writer has had the exceptional opportunity of supplementing his previous knowledge and personal experience of this subject by attending the excellent lectures and demonstrations of Dr E C Faust Dr J S D'Antoni and other members of the staff of the department He must however assume full personal responsibility for his interpretation of this teaching

The writer s special thanks are due to Brigadier G Covell C I E I M S Director of the Malaria Institute of India and to Dr R Kirk of the Sudan Medical Service for going through the final drafts of the malaria and sleeping sickness sections respectively for pointing out errors of fact and for making constructive suggestions While it was possible to make corrections and to take advantage of the suggestions it was not possible to send the proofs to these officers for final approval and the writer must assume full responsibility for the correct interpretation of their suggestions

For reading the page proofs of this edition I am very greatly indebted to Miss Joan McAllister and Dr David Weinman who kindly volunteered to undertake this task when I had to leave for Europe on very short notice

I am extremely grateful to The Macmillan Company who undertook the publication of this book during very difficult times and especially to Miss Marie Ranzini on whom a grave responsibility devolved while this edition was in process of manufacture

INTRODUCTION

THE EMPHASIS IN TROPICAL MEDICINE

Soon after Japan entered the war a number of army medical officers arrived in India from Great Britain and the United States and in order to initiate them into medical practice in the tropics classes were organized It fell to the writer to conduct some of these classes By way of introduction to his lectures he attempted to analyse the difference between medical practice in temperate climates (for which most of these men had received

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it would only be a matter of extending one s reading to include the rarer tropical diseases that are usually omitted from the more concise textbooks of medicine He believes that the main difference lies rather in the special emphasis given to certain aspects of those diseases that are looked upon as

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of these and it will
hich they are usually

presented rather than in the order of their importance

History—Tropical medicine is a young, rather self conscious branch of medical science much of its history has happened within the lifetime of the older of the present day writers and even though these writers may themselves have played little part in the historical events they often knew the principal actors personally But this emphasis on history is more than

istory of a disease and of the di
background for the proper appre
which must never be looked upon

as final however complete it may appear to be

Epidemiology—The diseases of Aberdeen are much the same as those of London or even of New York Berlin or Vienna and although respiratory diseases may be more common in the winter and certain infectious diseases at other seasons there is no sharp segregation to any one time of year of the bulk of the diseases with which the practitioner in temperate

of each disease so that one knows how where and when to expect to encounter the disease and does not lightly diagnose kala azar in central Africa sleeping sickness in India plague in the Punjab in July or sand fly fever anywhere in the northern hemisphere in January Other environmental factors also assume a far greater importance in tropical than in

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Ætiology and prevention—The bulk of the disease that one encounters in temperate climates are degenerative or chronic inflammatory diseases the prevention of which is outside the scope or even the thoughts of

the average practitioner, so that he has no further worry on this score, and, even when he does encounter an infectious disease, whether it is measles, influenza, or just a common cold, there is seldom much mystery about the mode of infection, which is usually by direct contact and/or droplet infection He has only the household, or, in the case of an institution, the other inmates to consider, and, after that, the most he need do will be to notify the local medical officer of health On the other hand, nearly all tropical diseases are of an infective nature and eminently preventable, so that the practitioner s thoughts should be for the community as much as for the patient He must have a thorough knowledge of the ætiologies of the

vector, an intermediate host, and/or an animal reservoir of infection In fact with few exceptions, notably diseases due to the direct effects of a tropical climate, nutritional diseases, and the intestinal fluxes, the vast majority of tropical diseases are transmitted to man through the agency of an animal and/or an insect

This is the type of problem that the practitioner in the tropics may have to face Is it Weil's disease? If so, he will think, it would be interesting to know how in this case the infection was acquired, and whether there was an occupational association, but he should know that in the

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ngue sea-
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disease has not appeared in the locality before then he must give his full attention to averting a major disaster After putting the patient under a

immediate thought So perhaps most of all, the practitioner in the tropics must have a thorough knowledge of the ætiology of all the diseases he is likely to encounter

The writer has always felt that the tropics provides a field in which the physician and the public health worker can meet most easily and naturally The physician is so often compelled to think in terms of prevention and the health officer has so often to invoke the aid of the physician to organize specific treatment campaigns as a means of limiting reservoirs of infection whereas they are nearly always mutually dependent on one another for accurate diagnosis

Signs and symptoms' *versus* laboratory findings—The populations with which one has to deal in temperate countries are usually relatively

When the Cumberland miner gets
much the same course as it would in a London banker, and it is possible to give a clinical description that will cover both cases It is not so with the vast majority of tropical infections A patient may react to malaria infection in a hundred different ways, but the one common factor is the

presence of parasites in the peripheral blood Further, the answers given by the illiterate patient, even if the language and dialect difficulty can be overcome, are often misleading, so that one is compelled to lay less emphasis on history and subjective signs and symptoms and more on laboratory findings

as important and necessary to carry out routine laboratory examinations of, at least, the stools, the urine, and the blood, as it is in any climate to make a thorough physical examination and to examine the patient's chest even when most of the symptoms point to the abdomen

On the other har
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uncommon to find
Entamœba histolytica cysts in the stools of a patient in whom kala-azar
uncture Although each finding might
there may be, in the particular case,
to these infections, and although in
most instances one would attempt to free the patient from his hookworm and amœbic infections during his convalescence after treatment for kala-azar, return to normal health may be possible without the eradication of either of these infections Nor does the discovery of all four of these infections exclude the possibility that the patient has some other disorder, such as a chest full of fluid, that demands immediate relief

Laboratory findings may be as misleading in some cases as they are useful and even essential in others, and, although the writer is in favour of routine laboratory examinations whenever it is possible to carry these out, it is very necessary that the findings should be given their proper perspective, viewed in conjunction with the whole clinical picture, and interpreted intelligently The writer's early experience of tropical medicine was all in the laboratory Even in those days he saw the danger of the complete laboratory domination of tropical practice, and he has fought very hard against this tendency ever since He hopes that in this book, whilst emphasizing the great importance of the laboratory, he has succeeded in keeping it in its proper place

Specific treatment —Finally, in the matter of treatment, tropical medicine undoubtedly stole a march on the mother science We had specifics for malaria, kala-azar, sleeping sickness, and certain helminth infections, not to mention the tropical spirochætal infections, when 'temperate' medicine could claim only salvarsan, unless one includes antivenine and diphtheria antitoxin one for each side The vitamins, penicillin, the sulphonamides, and other new therapeutic substances have gone some way to even up matters but, case for case, specific treatment is far more important in tropical than in temperate medicine Moreover, in tropical practice, conditions are often such that specific treatment is the only treatment that can be considered, and it is therefore given special emphasis It should, however, be appreciated that general and symptomatic treatment may be almost if not quite, as important as specific treatment If the writer on tropical medicine appears to neglect this aspect, it is because he assumes that the reader already has a sound knowledge of the general principles of medicine and expects that he will apply them It is not because he wishes to diminish its importance

CONTENTS

THE

PRINCIPLES AND PRACTICE

OF

TROPICAL MEDICINE

GENERAL CONSIDERATIONS

The Genesis of Tropical Medicine—Present day scientific medicine was born and nourished through all its earliest stages in temperate western countries When the people from the western civilizations invaded the East in a military or a commercial sense or simply as scientific or dilettante travellers they found that the medicine practised in many of these countries was the crudest form of traditional folk lore though in others, such as India and China there were established systems of medicine which intrigued these western invaders and from which the doctors amongst them gathered some useful recruits to the pharmacopœias of their own countries

However, early in the nineteenth century the superiority of scientific medicine over
visitors but a
more practitior
from the West
support them in the style in which quite justifiably they demanded to compensate them for the conditions under which they had to live, medical schools and colleges therefore were founded in the tropical countries to train the natives of these countries in methods of scientific medicine

About the middle of the last century, it began to dawn on the still conservative mind of the practitioner of scientific medicine in the tropics that, whilst the medicine that he had been taught was very much better than indigenous medicine, as it was then practised, he was frequently encountering syndromes to which there was no reference, or only very misleading references, in his textbooks Amongst those who had the gift of being able to think ahead of their time and the energy to stir up others to take action with them, Patrick Manson stood out Many of his predecessors and contemporaries played their several parts, and books on the diseases of various tropical countries were written, but it was Manson who gave this study of tropical diseases a definite form, a new branch of medical science came into being, and rightly Manson is looked upon as the father of tropical medicine *Through his energies the London School* of Tropical Medicine was founded and for many years his book stood alone as *the* textbook on tropical diseases

Nothing succeeds like success, and the early successes in the field of tropical medicine, which may be typified by Ross's work on malaria, stimulated this new branch of medical science, and other schools of tropical medicine were founded in Europe and North America

From one point of view this awakening of interest in the study of tropical diseases had come too late, for already in certain tropical countries India in particular, in the medical schools and colleges to the founding of which reference was made above, western traditions of scientific medicine
ises were firmly established The
vho had never been in a tropical
conditions and the diseases that
the course of study were faithful

practice If he wished to gain special knowledge of how to treat these diseases, he had to go to London, Hamburg, or Baltimore

appreciated by many, but the remedy

this power was not vested in any central authority It was Leonard Rogers who already had a world-wide reputation for his many researches in tropical medicine, who saw a way out of this impasse and, with the encouragement and a considerable amount of financial help from the commercial communities and large industries won over the official opposition and founded the Calcutta School of Tropical Medicine, for post-graduate instruction and research in tropical diseases He hoped that in time the teaching in this school would have a leavening effect on medical education throughout India, and possibly in other tropical countries, not only in the final years of practical work but in *due course in the* physiological laboratories and possibly even in the dissecting rooms, and that when it had done its work and outlived its usefulness in this direction this school would remain as a centre of research and higher post graduate studies

This is the writer's explanation of the anomaly of a post-graduate school in a tropical country where instruction is given to the local practitioners in subjects which should have been those most emphasized in their qualifying medical course

Defining the Scope of ... tropical medicine from the body cor ... artificial, and one hopes only a temp ... ent day, separate it is and very cor ... arises, is it possible to define its scope? It is certainly difficult The problem

hesitates to give information that may be misleading but this state of affairs is changing The next question is, how far should one go into the subject of tropical hygiene? This brings one to a wider question of medical policy, namely, the past tendency to separate the present hesitancy, and the future decision (we foretell) to link much more closely prevention and relief in medical education and practice In his teaching of tropical medicine, the writer has solved this problem by laying special emphasis on the preventive aspects of specific diseases whilst leaving the subject of

for many diseases that are always looked upon as tropical diseases malaria, cholera dysentery, also occur in the temperate zones So we must fall back on an elastic definition and say that under this heading should be included diseases that occur only in tropical and sub tropical countries, and also diseases that are either more prevalent or else exhibit special features in these countries

The Changing Picture —The position is not however static Many diseases that were at one time world wide in their distribution are now confined almost entirely to tropical countries of these perhaps the best example is leprosy Leprosy was a cosmopolitan disease common enough in England a few hundred years ago as is evidenced by the leper windows that still exist in many old churches but it has now disappeared almost completely from most western countries Malaria has been banished from England and many other European countries and yellow fever from the east coast ports of the United States of America to become a disease with an essentially tropical distribution Cholera and plague have probably

It seems possible that tuberculosis is now going the same way as leprosy The 'white man's plague' has certainly changed its colour preference in America and has shown a steady decrease for nearly a hundred years in Great Britain, but it is rapidly increasing in many tropical countries, just as is cerebro-spinal fever another respiratorily transmitted disease, in the crowded bazars of the east

Diseases Uncommon in the Tropics—There are diseases that are less common in tropical countries, *e g* rickets, most streptococcal infections, erysipelas scarlet fever, and card
included in this category but is
A sterile controversy regarding
carditis in the true tropics has b
to time The champions of the former view made their point many years ago, but are tending to push too far their claims for the frequency of the occurrence of rheumatic carditis, relatively and, almost certainly, actually, it is a far rarer condition in tropical than in most temperate countries

Then, there are diseases that are *supposed* to be less common in the tropics, these include cancer, but it is very doubtful if this is really uncommon Statistics are vitiated by the infrequency of post-mortem examinations, by poorer diagnosis and poorer facilities for treating the patients when a diagnosis is made, by a much lower expectation of life so that far fewer people reach the cancer age, and by the fact that the numerous other diseases that occur distract attention from cancer as a public-health problem, except in a few instances where its cause is patent, *e g* *kangri*-burn cancer of Kashmir Enteric was another example, sixty or seventy years ago, there were many discussions in the medical journals as to why enteric occurred amongst British soldiers in India but never amongst the indigenous inhabitants, until bacteriology came along and taught us to recognize as enteric the slightly modified disease that is very common amongst Indians

ENVIRONMENT AND THE DISTRIBUTION OF DISEASE

There are of course many [illegible] ases that are inexplicable in our presen [illegible] he exact ætiology of these diseases but [illegible] have been collected over a period of mar [illegible] some of the factors that determine the distribution of diseases in tropical and in non-tropical climates, these factors can be classed as (*a*) climatic, (*b*) telluric, and (*c*) human

A **Climatic factors**—Climate is brought about by a combination of solar and terrestrial influences, though it is with the sum-effects of these influences that we are concerned, they must be considered first under a number of different headings —

(i) Temperature—This cannot be expressed as just hot or cold for hot climates exhibit wide variations in their temperatures and these temperatures cannot be given simple numerical expression there are climates that are hot *throughout* the year and others that have a very hot and a very cold season, some countries have a temperature that shows little variation during the twenty four hours of the day, others one that whilst it is extremely high during the day drops very considerably at night and yet others that exhibit both these features but at different times of year *To convey a proper idea of the temperature of* a locality, a full range of 'normal' data for the whole year should be given, but if it has to be expressed very concisely the best figures to give are the mean of daily means and the mean diurnal ranges for the hottest and for the coldest months of the year

(ii) Humidity—This is expressed as —
- (*a*) absolute humidity in grains of moisture per cubic foot
- (*b*) relative humidity, indicating the percentage degree of saturation, *100 per cent being complete* saturation at the existing temperature
- or (*c*) saturation deficiency, which indicates the drying power of the air expressed as the difference between the vapour tension at dew point and the actual vapour tension at the time in millibars

In one country there are wide differences in the humidities in different localities, from season to season and at different times of the day, the early morning

humidity, which is the one so often given, is always high and gives a very poor indication of the humidity of a place or a season

(iii) Air movements and prevailing winds —This is recorded in miles per hour or feet per second two miles an hour being roughly 3 feet per second In the matter of wind prevalence, an important factor is usually whether the prevailing wind is from the land or the sea, but there are many other considerations too numerous to indicate here

(iv) Sunshine —This is recorded as the number of hours of sunshine during the day This important factor appears to receive more attention in weather reports in temperate and cold climates

(v) Barometric pressure —Whilst this is subject to considerable irregular fluctuation localities of the same altitude above sea level do not show constant variations that would be likely to affect disease distribution However the has an effect on physiology and

t variations according to the ear it is expressed in inches per

tant factor in the make up of a climate both in temperate and tropical zones Though storminess in temperate zones is associated with respiratory disease and rheumatism on the whole the balance is in favour of the stormy climates and Huntington (1924) goes as far as to say that it is the northward shift in the storm belt that has caused the northward and westward shift in the centres of civilization a view not in keeping with that expressed by the writer (*vide infra*)

A factor associated with this is atmospheric ionization and some medical climatologists attribute much in the balance of health and disease to this Our knowledge on this subject is at present too vague to allow any helpful discussion on this factor

B **Telluric factors** —These can be considered under two headings —

(i) Natural —The physical and chemical nature of the soil the sub-soil water level vegetation etc and the physiographical configuration of the terrain

(ii) Artificial —Irrigation and drainage afforestation and deforestation the building of cities (that shut out air and hold the heat) etc

C **Human factors** —These include the density of the population and the degree of urbanization, and industrialization to which they have been subjected [illegible]

populations

Variations in these climatic telluric and human factors from place to place will determine the geographical distribution of disease, from year to year their epidemic occurrence and from season to season their seasonal incidence Nearly all these factors are interdependent and, as they never act singly, it is seldom possible to judge the effect of one alone—*e g* the effect [illegible] taking account of the hum[illegible] re of the soil, etc , and the [illegible] and purity of the atmosph[illegible] the various factors are not [illegible] a in the Punjab is depender[illegible] holera

[illegible]

CLIMATE AND DISEASE

How do climatic conditions prevalent in the tropics bring about tropical diseases? They act directly and indirectly

A **Direct effects of climate**—The compensatory mechanisms of the human organisms are so elaborate that the direct effects appear to be remarkably few, this is shown by the fact that the physiology of man living in the tropics is basically the same as that of man living in the arctic zones There are certain immediate reactions to change to tropical climatic conditions that are rapidly adjusted or compensated These can be imitated in the laboratory or ward, have in the past been studied frequently, by physiologists, and are now, since the introduction of hyperthermal methods of treatment, receiving the attention of clinicians At the other end of the scale, time measured in centuries produces certain fundamental changes in the human frame which are of interest to ethnologists, but here one is uncertain whether the effects of climate producing these have not also been indirect, through diet and other environmental factors Between these extremes there are the results of the subjection for months, for years, and for generations to tropical climates, *and it is these that are of special interest to the physician* Beyond the observation and explanation of certain obvious differences between the inhabitants of the temperate and tropical countries, such as that of colour, the subject of tropical physiology has been neglected, and until this gap in our knowledge is better filled, we shall find our study of the pathological effects handicapped

The sun's rays—Fundamentally the cause of the difference between tropical conditions and those of the temperate zones is the fact that the rays of the sun are more direct and therefore, other things being equal, produce their effects with greater intensity in the tropics, it will thus be appropriate first to consider what are the direct effects of these sun's rays on the human body These effects can be classified according to the different rays which strike the earth, thus —

	Spectral classification	Effects	Angstrom units		
1	Ultra violet	Biochemical rays	1 000	-	3 900
2	Violet		3 900	-	4,300
3	Blue		4,300	-	5 000
4	Green	Luminous rays	5 000	-	5,600
5	Yellow		5 600	-	5 900
6	Orange		5 900	-	6,200
7	Red	Heat rays	6,200	-	7 700
8	Infra red		7 700	-	120 000

We have very little data regarding the relative power of the **ultra-violet rays** in tropical and non-tropical countries, but usually there is less interference with these rays in their passage to the earth's surface in the *former* and their effect is therefore greater The ultra-violet rays have
a low power of pen
skin and subcutane
their action on erg
layers of the skin,
children in tropica
children are unduly protected from exposure to the sun

On the skin, the most noticeable effect of the ultra-violet rays is an erythema which comes on two hours after the exposure and reaches its maximum in about six hours, this will vary in its severity and in extreme cases will lead to severe blistering Repeated irritation by exposure will

lead to chronic changes in the skin (*vide infra*) The wave le
produces this erythema is from 2 800 to 3 100 A

The natural pigmentation in the skin of the indigenous inhab
the tropics acts as a protection against this effect of the ultra vio
and even amongst the white races the brunette is usually less s
than the blonde The pigmentation that follows repeated expos
the sunlight is brought about by rays of slightly longer wave
including the visible rays

The unhealthy pallor of the skin that is often seen in the Eur
sojourner in the tropics is due to the excessive zeal with which he—or
often she—has protected himself from the beneficial sun s ray comb
with unhealthy living and in many instances disease

The luminous rays again are usually stronger in the tropics t
powers of penetration are greater than those of the rays of shorter wa
length and they probably have a stimulating effect on the blood a
tissues as well as a detrimental effect on parasitic micro organisms b
our knowledge on this subject is more speculative than precise The
action on the retina is more certain in excess they cause headaches
reduction in visual acuity a decrease of adaptability to comparative
darkness which may become pathological in special circumstances (night
blindness), and other pathological changes in the retina

However probably the most important are the *heat rays* both the physiological and the pathological effects of the heat rays on the body temperature have been studied in rather more detail than have the physiological effects of the other climatic factors Before considering the effect of heat rays, one must review the physiology of heat balance

Heat balance.—Heat is produced by the cellular combustion of foodstuffs Only some 20 to 25 per cent of this heat is converted into energy and the balance has to be dissipated If this heat is not dissipated the body temperature which in man and other warm blooded animals is normally maintained at a constant level will rise and the physiological processes of the body will be interfered with To maintain this constant level there must be a balance between the heat that is produced by the metabolic processes of the body and the heat that is lost to the surroundings Under tropical conditions the rate of this heat loss is reduced and there are times when the process of balancing the heat account is complicated by the fact that certain items that are normally on the debit side are now transferred to the credit side of the account i e when the atmospheric temperature is higher than that of the body and heat is actually absorbed from the environment

Heat production.—In an average man (whose weight is usually placed
t 70 kilogrammes or 154 lbs though the figure is too high for the
ndividuals of many races e g southern Indian average weight about
20 lbs) normal body functions produce about 100 calories an hour at
st work accelerates heat production and a soldier marching with a pack
ighing 65 lbs will produce 8 calories per minute

Heat loss.—Heat is lost by radiation conduction convection and
poration For practical purposes the means of heat loss can be
idered as 'sensible' loss which includes radiation and conduction to
ounding cooler objects and convection that is loss to the air in contact
the body surface—this air absorbs heat moves away and is replaced
ore air when the process is repeated—and *latent* loss which is achieved
saturated air absorbing moisture from the body surface from the

Finally, *beyond this 'discomfort zone'* conditions are encountered under which man cannot survive for any length of time without his temperature rising, the hyperpyrexia and shock that may result from subjection to such conditions must be considered under the heading of 'diseases due directly to climatic conditions' (*vide infra*)

Other Physiological Effects—Some of the effects of tropical climatic conditions on other body functions and systems can be briefly reviewed

A change to a tropical climate is accompanied by an increase in blood
...which is apparently a dilution for
. corresponding relative reduction
...rmed elements are concerned, is
little evidence that the increased
...n to heat equivalent to that
frequently encountered in even moderate tropical climates will lead to a temporary increase in pulse rate (*see* figure 2), but the normal pulse rate of the inhabitant and of the sojourner in the tropics (this term is used in reference to those who normally live in a temperate climate but are temporarily living in—not just travelling through—a tropical country) is about 75

The blood pressure of the sojourner is apparently not materially changed by residence in the tropics, though possibly low blood pressures are more frequently encountered than in temperate climates On the other hand that of the indigenous inhabitant is distinctly below the European and American standards (Cadbury, 1922, Kean 1941)

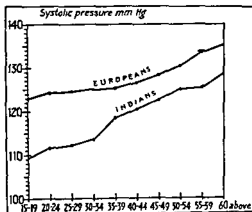


Figure 3 Blood pressure of different age groups

than the European standards at

southern and eastern Indians (from Madras and Bengal) Meat eaters showed pressures 1 to 2 mm higher than the pure vegetarians

The respiration rate after acclimatization is apparently slightly decreased but the volume of each breath is increased There is—judged on balance of conflicting evidence—a slight decrease in the normal **basal metabolic rate**, and this corresponds with the lower calorie requirement of the tropical resident

...to high temperatures is said to depress **hæmopoietic function**
The 'thin'
...nal standards
closer to the
...ably higher)
higher than
and the normal range amongst white sojou...
even the American standards (Napier and Das Gupta, 1942) The higher

hæmoglobin normals at high altitudes is recognized as a compensatory mechanism and it is probable that a greater oxygen carrying power of the blood is necessary to counter balance the lower oxygen tension in the hot air of the tropics

Moderate heat will cause a rise in the **leucocyte count** (*see* figure 2) but this is apparently not maintained for the average leucocyte count in tropical residents is certainly not higher than in residents in temperate zones There is however evidence that the stimulation of the leucopoietic tissue is maintained for there is a persistent shift to the left in the Arneth count indicating a more rapid turnover of polymorphonuclear leucocytes which in many cases is unassociated with infections There is also a persistently higher eosinophil count but it is impossible to exclude causes other than the climatic conditions for this

cooler climates and consequently fail to rise to the occasion in diseased conditions There is some effect on the sex glands for on the whole the inhabitants of the tropics tend to reach sexual maturity earlier and they are certainly liable to an earlier decline Mills (1941) takes an opposite view and quotes figures in support in which he shows that Panamanian

The sex urge of the sojourner is popularly supposed to be stimulated on arrival in a tropical country but it is possible that this is a false impression created by the reduced opportunities for legitimate and the increased opportunities for illicit relief

The digestive functions—independently of food requirements that are slightly but distinctly lower especially with reference to fat and protein—

writer and his co workers the statement frequently ropics in our experience in British and American condition of the gastro intestinal tract is commoner amongst sojourners especially women than amongst the same persons living in cool climates but there is little evidence of this in the local inhabitants and it is difficult to exclude bowel infections as the cause The hyperæmia of the skin induced by a hot climate may lead to an ill distribution of blood and a relative ischæmia of the digestive organs with resultant hypofunction

iate *per se* are hard ctors The nervous hite sojourners is themselves to local evidence of this in the indigenous population or in the more moderate and more adaptable sojourner Similarly there is little evidence that tropical neurasthenia is a direct climatic effect though here again the monotony of the tropical heat

fails to provide beneficial periodic stimulation Failure of memory, which is referred to as West Coast memory, Bengal head etc, according to the locality, though it is common in all tropical countries, is probably more result of the environment and the circumstances than actual temperature and may be a manifestation of a mild form of neurasthenia, associated with inability to concentrate On the other hand, neuralgias are certainly less evident in a hot than in a temperate climate

There is no evidence that ultra-violet rays of the sun have any direct action on the brain or spinal cord, they do not in fact penetrate even the skin, and certainly not the skull But the visible rays may have an effect on the retina causing a temporary and in certain cases a permanent reduction in visual acuity and also night-blindness (*vide supra et infra*) these changes may react constitutionally and produce headaches, vomiting and other symptoms often wrongly attributed to the direct action of the ultra-violet rays on the brain and cord

The evaporation mechanism of the inhabitant in the tropics is attuned to the local conditions, and their 'invisible' perspiration is much more effective in keeping down body temperature than the profuse and wasteful perspiration of the sojourner this helps to explain the greater frequency of heat ill-effects in the latter (Lippmann, 1942)

The continuous hyperæmia and moistness of the skin in the tropics probably does not actually produce any pathological change, but it tends towards the blocking of the sweat glands, it allows certain infections to establish themselves more easily, and possibly it prevents others

Pathological changes —When the compensatory mechanisms of the body fail or when the changes brought about by extreme environmental conditions have passed beyond the physiological limits the conditions produced must be *classed as diseases (vide infra) caused by the direct effects* of climate

B **Indirect effects of climate** —Whilst the direct effects of tropical climates can be dismissed in 2[illegible] the subject matter for the rest of this book [illegible] ical climate are determined by the nature [illegible] n determine the state of nutrition of the [illegible] iencies that prevail amongst them (*b*) of the bacterial, protozoal and helminthic *parasites that are the causal organisms of disease*, (*c*) of the insect life that transmits these causal organisms to man and/or (*d*) of the animals that carry or act as reservoirs of infection, or climate acts, (*e*) by favouring, or the reverse, the natural enemies of insect vectors and animal reservoirs of infection, and (*f*) by determining the balance of biological competition amongst insects, fish, birds and mammals

Theoretical —There is scarcely any limit to the indirectness of the ways in which climate may react on the distribution of a disease and the important climatic factor may appear at first sight to have as slender a connection with the particular disease as the cow *with a crumpled horn had with the house that Jack built* For example the normal climate in a locality might favour a certain crop that was parasitized by an insect that was the main food supply of a bird that fed alternatively on another insect that was the transmitter of a human disease A bad year (climatically) might lead to the failure of the crop which one would expect would lead to a dearth of the parasitizing caterpillar so that the bird would have to turn its attention to the disease transmitting insect with the resulting fall in incidence of the human disease

The effects of climate may thus be not only indirect but very complex and difficult to explain If to follow the hypothetical case given above one wished to explain the decrease of the disease on the climatic factor it would not be safe to assume any single step in the effects and counter effects it would be

essential to ascertain whether unfavourable conditions to the plant did in fact cause a decrease in the caterpillar population, or whether, as often happens interference in the nutrition of a plant led to an increase in parasitization, whether the birds actually were induced by shortage of their primary food to feed on the d[illegible] ether in fact they were driven away to [illegible] en in the presence of a surfeit of [illegible] take their quota of the disease-carrying [illegible] ble epidemiological effects of certain climatic factors are dangerous and as often as not have to be reversed when actual investigations are carried out

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MEASURES FOR MITIGATING THE EFFECTS OF TROPICAL CLIMATE

Introduction —The early civilizations were all in warm countries, here primitive man found food plentiful and life comparatively easy, so he had [illegible]

cooler climates, and the centres of [illegible] we are learning how to control our environment in hot climates also, and it seems possible that this drift may be stopped or even reversed

The history of civilization has been described as the story of man's [illegible]

Here we are concerned especially with a tropical environment and we have discussed above the ways this may influence the health of man The effects may be direct or indirect The major portion of this book is devoted to the indirect effects, to the means by which we can counteract these before they produce diseases, and, when we fail in this, treat the diseases that are produced In the previous chapter, the direct effects of the tropical environment were discussed, the present one will be devoted *to the mitigation of the direct, and in a general way the indirect, effects of* the tropical environment by the adaptation of man to this environment and of this environment to man

The subject will necessarily be considered more from the point of view of the foreigner, as the local inhabitants will already have achieved a degree of adaptation, especially to the more obvious direct effects Their practices should be studied but never adopted without critical examination as they are quite frequently unsound, further, they are seldom directly ... become habituated ... trous, our special ... plied, and, finally, the amenities that recent ... given us must be superimposed

... A very great deal that has been written on the ... dependent on analogy and guess-work, ... he guess-work will have to continue to ... idually more susceptible to temperature changes, are by a process of natural selection capable of acclimatizing themselves slowly to changed conditions, but the process takes many generations in the more complex and more adaptable human individual, the same process will take many more generations, so that racial acclimatization is measured in millenia

Individual acclimatization is largely a matter of the adaptation of ... evidence that by ...

his general behaviour are less suited ... the indigenous inhabitant

What are the usual reactions of the European or North American who spends the best part of his adult life in a tropical country, to the heat?

The first year he usually finds particularly trying, but he learns how to adapt his habits, and settles down, taking the climate as he finds it, though naturally grumbling in the hottest weather, for the next 15 to 20 years, after this he finds each hot weather more and more trying and the thought of retirement dominates his mind, unless he can get away each summer There are of course other factors, such as disease and age, but at least the effects of acclimatization are not very apparent

... in the British ...

amongst British troops under ... some extent due to racial acclimatization, but even here other ...

disease and behaviour, cannot be entirely ignored, heat trauma is seldom uncomplicated and is usually induced by some febrile infection, such as sandfly fever, to which the Indian soldier is more likely to be immune

The Indian coolie will exhibit his 'pathetic contentment' and not complain of the heat, but it has been the writer's experience that the loudest complaints a
European but from
'comfort zone' in a
of the Cantonese cl
of the staff

It will be apparent therefore that the question of acclimatization is not altogether a simple one and that data are urgently required

INDIVIDUAL HYGIENE

Diet.—The nature of the food taken plays a fundamentally important part in the maintenance of health of the individual and in determining the nature of the diseases from which he is likely to suffer, and in some cases food is the main, if not the only, factor in the production of a specific disease In investigating a disease in an individual, a rough—if circumstances preclude an accurate—idea of both the food taken recently and the usual diet of the patient must be ascertained, or, in the case of a community, a knowledge of the general diet, and any special deviations that have been associated with the disease, are essential

The subject of the dietetic requirements of the indigenous inhabitants of the tropics, and of the diseases associated with dietary deficiencies will be discussed elsewhere, here it is proposed to make a brief reference to the dietary requirements of the sojourner
diet is a matter of such fundamental
health in the tropics, why be so brief a
is that conditions under which the sojo
tropical countries that specific suggestic
call forth the derision of a majority of readers, that accurate data for even single sets of conditions are rare, and, finally, that this is not a book on dietetics or housewifery

The dietary requirements in the tropics are distinctly lower than they are in temperate climates This applies both to the sojourners and to the indigenous inhabitants A very large number of the latter are vegetarians and though many of the diseases from which they suffer can be attributed directly or indirectly to a deficient diet, which a diet solely vegetable in origin is very liable to be, a well-selected vegetarian diet is certainly better suited to the local conditions than the heavy meat diet that many inhabitants of the temperate climates take

The sojourner will maintain better health if he reduces his meat meals to one a day The protein requirements are lower, but if he does not exceed the traditional 100 grammes, further restriction is probably unnecessary, on the other hand, *it will be wise to cut down the fat to 70 grammes a day* Fruit should be taken at every meal when fresh fruit is available, and when not, tinned fruit at at least two meals, and as large a variety of vegetables as is obtainable

The general principles greater
care in the tropics than els ns that
are about, ready to atta is not
maintained at its peak in, but
asceticism is often carried too far

It is of course essential that all the vitamins should be well represented in the diet The most common deficiencies are associated with vitamins B complex, C and A in that order, and iron In an ordinary mixed European diet and in the ordinary diet of the well to-do Indian, none of these
prescribed T
the tropics f
medicinally, a
of concentrate

Constipation is a common complaint amongst sojourners in the tropics, even more so than it is in their own temperate climates, it is enhanced by the dehydration that is likely to occur unless plenty of fluid is taken, and by the tendency of the jaded appetite

purgatives

Sp
its pre
with p
placed
prelim
to prot
and s
fruit'
regard
fact—
is a v
of a grape fruit that has been kept cut side downwards overnight in an electric refrigerator Similarly, twice cooked food whilst best avoided, as each cooking lowers its vitamin content and usually its digestibility, need not be looked upon as a positive danger in these days of electric

or
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tr
a
d
th
ir
water and the washing of salads and fruit so that it can be checked *any* day, even if he does not check it *every* day

The kitchen or cook house, far too often a ramshackle outhouse, is the one room in the establishment over which the greatest sanitary care should

be exercised (*vide infra*). It is not always possible to have a white-tiled kitchen, but a high degree of cleanliness can be attained without this refinement Above all it should be inspected regularly, and also at odd [illegible]

complaining at the same time that they find it difficult to fill their day When such w [illegible] housekeeper a [illegible] adjust thems [illegible] new conditions, but this is more often the pose of those who never saw a domestic servant in the homes from which they originated

Another matter closely associated with food is the servants' dusters, tea-cloths, glass-cloths, dish-cloths, etc Native servants will, if possible, convert anything that is given to them into an all-purpose cloth, which in addition to the above functions will be used for mopping their brows, wiping their noses, straining the soup, and finally, when cold drinks are demanded, for breaking ice in The potential dangers of such a practice are more [illegible] eral [illegible] e g [illegible] the [illegible] the [illegible]

Much preventable ill-health amongst the sojourner is directly attributable to the 'studied' indolence of their women, and the writer regrets that those of British origin are apparently the worst offenders*

Beverages and Alcohol

The question of what to drink, which may be an unimportant one in temperate climates, looms very large in a tropical country, because, when evaporation plays such an important part in maintaining a normal body temperature, the physiological requirements of water are much greater Not only should one's thirst, which is the outward and visible sign of water depletion, be satisfied, but a definite amount of fluid should be taken as a routine, for example, it is a good plan to drink a glass of water on rising in the morning In hot dry climates, when moisture depletion is considerable, it should be remembered that a considerable amount of salt is also lost in perspiration and that this is not replaced by water, so that it is a good practice to make a habit of taking a tablet of at least 10 grains of sodium chloride with each glass of water

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[illegible]

The greatest obstacle to teetotalism in the tropics is the absence of a 'soft' drink that is really acceptable to the male palate. The 'windy insufficiency' of these is more than an excuse, it is very frequently the reason, for the resort to beer or whiskey and soda to quench an honestly earned thirst. It is of course unnecessary to drink gaseous lemonades or to add soda to sweet drinks, but even drunk 'still' they are very nauseating to many people. There is of course nothing more refreshing

the refrigerator, if the taste of the water

There is also very much to be said

y, and taken after the day's work its

to put off the hour when the whiskey

erly made can be a very good drink,

ffee is more popular. The neat juice of citrous fruits such as oranges, grape fruit, lemons, or limes, which are often abundant and cheap probably make the best long drinks and are an important source of vitamin C, and tomato juice has been the salvation of many, particularly women, who do not like to refuse to drink, but dislike alcoholic cocktails.

About alcohol, it is not possible to lay down any hard-and-fast rule. The pernicious fable that it is necessary to take alcohol every night 'to ward off fever' is happily dying, but alcohol, taken in strict moderation, in the evening to ward off depression that often follows the sinking of the sun is a valuable psychological stimulant. For this and other reasons the writer would hesitate to recommend teetotalism to the white sojourner who with his parents before him has probably been used to taking a moderate amount of alcohol, except in the case of one who has already shown instability in this matter, or who has a family history of dipsomania.

working capacity.

Regarding the safety of drinks taken outside one's own house, it should be remembered that converting water into soda-water does not sterilize it, nor does the addition of alcohol, in the strength in which it is drunk in the ordinary whiskey and soda, make doubtful soda-water safe. Where a drink has to be taken in a strange place, the only safe drink is coconut water, and this is better drunk directly from the shell than from the *very doubtfully clean glass that is often offered to one*. It is also incidentally as refreshing a drink as any non-alcoholic drink that the writer knows.

Of the alcoholic drinks, whiskey with soda, or better still with water, is the best long drink, and gin and lime juice or bitters, not too 'short', the best cocktail. Mixed cocktails are not to be recommended. Light beer is quite a good drink, but does not suit everybody, and wines do not usually keep well in the tropics, but half a bottle of wine, red or white, with the evening meal, *instead* of spirits earlier in the evening, may be taken without detriment by those who prefer to drink with their meals.

Work and Leave

Western sojourners in tropical countries have brought with them many of their own habits, and amongst these is a restless energy that expresses itself by observing much longer hours of work than the indigenous inhabitants in many countries were previously accustomed to, including working through the heat of the day There is much to be said against this practice, and, except in large towns where workers live a considerable distance from their work and where therefore a mid-day interval would be of little use to them, it is wise to arrange the working hours in such a way as to take advantage of the comparative cool hours in early morning and evenı ... ddle of the day for rest ... two and three o'clock in ... o'clock in the morning, six hours of work can be done before mid-day (that is, 2 to 3 hours before the peak is reached) and the rest of the day's work in the comparative cool of the evening

Whilst a full day's work is certainly not to be discouraged, every ... or at least a different, ... rules allow the accu- ... f one's service This ... view of the framers, ... tired rather than a ... part of the individual ... ks down and he does ... -year spells are the ... home' leave in most ... etween leaves should ... e possible and senior ... possible, for the sake ... lls of work should be punctuated by short breaks of even as little as ten days, whenever this can be managed, and the doctor should take every opportunity to order ... ntal torpor into which ... it getting away for a ... no valid reason, this ... making the necessary arrangements

Exercise, Rest, and General Habits

... than in temperate ... finds that walking ... a little cycling or ... self in reasonable ... ires a little more ...

... l at the other end ... n one is very tired ... certain amount of ...

that the need for regular exercise requires to be ...

with the latter exercise is frequently a fetish and is more often overdone than neglected It is a common fallacy that the early morning exercise expiates the sins of the previous night Though there are individual variations in the matter of exercise requirements, just as in everything else, it is very largely habit and/or gastronomic and alcoholic excesses that lead to the remark so often heard from the sojourner 'I must have my morning exercise, or I cannot get through my day's work'

Another fallacy is [illegible] can be controlled by exercise alone Figures worth [illegible] effects of only two lu[illegible] five hours of strenuou[illegible] required to dissipate [illegible] that, if he cut down his [illegible] evening meal to two [illegible] ot only would he feel [illegible] rly so tired at the end [illegible] -health is not the fault [illegible] ibits The majority of [illegible] prematurely), but the [illegible] irlier

Exercise should be graded according to age—football, hockey, hard singles tennis, and squash rackets are for the young, cricket and mixed tennis can be continued into the forties, after which golf is the game of choice Riding can be graded to suit all ages, and walking and swimming are always useful alternatives, the last-named being particularly valuable in special conditions such as pregnancy

As important as exercise is rest. The traditional mid-day siesta is not observed by the majority of sojourners who have their livings to earn, and, except in very hot climates where there is a mid-day break in the daily routine, it has little to recommend it, though for children nearly always and for women in many circumstances, it is a good practice

There is probably no single factor more important in the general maintenance of health than a good night's rest, and, as it is difficult to sleep after about 6 30 in the morning in most tropical countries, early retirement to bed is essential (*see* p 30)

On the whole, smoking is probably more detrimental to health in the tropics than elsewhere This may be because cigarettes and cheroots are the more common media than the less detrimental pipe Idle and neurotic women are particularly liable to become 'chain smokers' It is more frequently on account of gastric disturbances than the toxic action on the heart that one has to recommend abstinence from this practice There [illegible]

Finally, advice on personal habits can be summed up in the simple counsel—admittedly one of perfection—moderation in all things

Clothing

In the matter *of* clothing, *it is probable that we can add little* to time-honoured local practice, the very scanty clothing of the South Indian coolie and the light loose clothing, easily thrown off the shoulder, of Indians of the educated classes are eminently suited to the hot damp

climate of southern and eastern India, just as the *burnouse* of the Arab is to the much greater but dry heat of the desert The 'actinic-ray-proof' red lining of the khaki coat is just trade propaganda to sell an article ill-adapted to most tropical conditions

The pictures of heroic scenes during the Indian Mutiny fill the present-day observer with horror, not a
practised by the rebels, but because of
soldier by the army authorities who
The khaki drill that replaced this was a distinct advance, but it seems to have taken the present war to break down old traditions and allow the adoption of the sane and sanitary, but one must admit slovenly, dress of *the soldier of 1940*

The civilian sojourner in the tropical metropolis is following this example rather slowly, as individual conservatism is harder to break down than official conservatism in a matter of this kind, but one hopes that the 'bush shirt' or some other form of open-necked short-sleeved garment will be the accepted 'office wear' before many more hot weathers have been endured

The essential features are that clothing should be light in colour, so that it reflects the maximum and absorbs the minimum of heat, light in texture and open woven, so that moisture-laden air is continuously carried away from the body and replaced by drier if not cooler air, and light *in weight and loosely fitting, so that it does not weigh heavily on the* shoulders, and hips, or cling round the neck, legs and wrists, but, again, allows free circulation of air and thereby evaporation

It is not possible to lay down any hard-and-fast rules for Europeans' clothing in the tropics, as conditions as well as customs vary so widely For general comfort and efficiency, where appearance and convention may be ignored, shorts and a shirt open at the neck (preferably white but light khaki is more serviceable), the former made of a light drill and the latter of light longcloth or an open-woven cotton material, will be the best, under this a very fine cotton vest and a pair of short trunks, of the kind that give some support to the scrotum, add to the comfort without adding much to the weight

In the ordinary way, the shorts should be cut to rest on the hips,
and in
ust may
rt The
n to the
careful
r ticks,
limates
es such

coat immediately after a game of tennis, when
is 80°F and the chances of chilling are very slight, is both unthinking and unhealthy, it is far wiser to allow one's body temperature, which will probably be raised two or three degrees, to return to normal before putting on a wrap

The flannel **cholera belt**, whose powers of cholera prevention were of course mythical but which could be guaranteed to produce a nice band of prickly heat in most climates, has fortunately gone out of fashion

Quiescent abdominal infections are sometimes stimulated into activity by local chilling which the cholera belt was designed to obviate, it is therefore advisable for those subject to attacks of diarrhœa to put their wraps round their abdomens, rather than over their shoulders, when cooling off after exercise

Long stockings that were at one time nearly always worn with shorts are now often replaced by very short socks that do not come above the ankle, or ordinary socks rolled to the ankle, these should be of cotton or silk *Women seldom wear stockings in these days*

'In the Malay States, they have hats like plates which the Britisher won't wear', sang the satirist, nevertheless, we have probably made some advance in the matter of suitable headgear and in most instances have improved on the local customs, though even in this there is a great deal of pseudo-scientific nonsense written and talked by the 'trade' The essential features of suitable headgear is that the brim should be wide enough—at least 5 inches—to shade the eyes and the back of the neck, be light in weight and colour, be held well away from the head, both at the brim and over the vault—air is an excellent insulator—and be well ventilated by generous openings to ensure free interchange of air These features are not incompatible with a headgear of reasonably æsthetic appearance from the point of view of male fashions, and a fantastic shape is no guarantee of a scientific conception

European women are recommended to adopt the 'severe' male style and not to attempt to disguise a pith foundation as a recent fashion model, the attempt is always a ludicrous failure

with a wide brim, is in most cases adequate from the point of view of interrupting the sun's rays, but neither is so well ventilated as the pith 'topee'

The protection of the eyes is more important than that of the head,

produce very severe headaches

Footwear again will depend on the circumstances It would be inadvisable to advocate canvas shoes for tramping through excreta-contaminated soil on tea estates, but for town wear they are far better than leather, in that they allow freer ventilation, 'co-respondent' shoes, made with white canvas in the place of buckskin, are smart enough for town wear and are an excellent prophylactic against 'foot-rot', *i e* tinea infection with septic complications (*vide infra*) 'Mosquito boots', with

high canvas tops, are useful for protection in the evenings in mosquito-ridden localities

HOUSING AND SANITATION

Much can be done to mitigate the ill-effects of the tropical climate by suitable housing The design of a building will naturally depend on
on economic considerations,
the average sojourner and
rements will of course vary
climate and on other local
considerations, on whether it is a hot dry climate or a hot damp climate, and whether in the latter case the rainfall is so high and the drainage of the soil so poor that it will be necessary to have the house raised off the ground, or, in extreme cases where flooding is common, built on high stilts, or conversely whether the damp rising from the ground into the walls of the house will be welcome as an aid to temperature reduction during the hottest time of the year, again whether the walls should be thick and the house built so that it can be hermetically sealed during the hottest parts of the day (as for dry climates), or whether it should be constructed so that the maximum fresh air will be available throughout the 24 hours, whether *it should be built to withstand heavy rainfall* or if this is so rare *that no allowance need to be made for it, whether it is to be in a town or in the* open country, whether it will be necessary to make the building mosquito-proof, or not, whether its rooms are to be artificially cooled, or whether cooling will have to depend on natural methods, and so on

It will be obvious that the subject of housing in the tropics is a very complicated one It has seldom been studied scientifically, except as a purely local problem to meet immediate requirements and is still almost entirely in the hands of the amateur, and often not a very intelligent one at that

When looking at an old house built a hundred or more years ago, in India for example, one often hears the sigh 'Ah, they knew how to build houses in those days' They did in fact use common sense and build houses with very thick ... ly
with broad verandahs to act ... at
and the large inner rooms, ... m
even if we wished to do so ... pt
himself to changed circumstances and if he has not been very successful he has the excuse that science has provided him with very few data
... Since modern tropical institutes are tending
*, one hopes that the subject will
that future writers on tropical
... depend entirely on the few crumbs
of scientific investigation, such as that of Crowden, the importance of which they have to exaggerate in order to disguise the poverty of the meal that they are giving to their readers

Present day trends —The general tendency today is to build the walls of the houses less thick than formerly, primarily because of increased cost, but the thinner walls, if insulated with the low-heat transmission material, have certain definite advantages over the old type of building with very thick walls

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* Mr B Dyer professor of sanitary engineering All India Institute of Hygiene and Public Health Calcutta has kindly supplied some of the data given below

In the old houses with walls 3 feet thick built of low-density brick and plastered inside with a difference of 10°F between the indoor and outdoor temperature there was a heat transmission of 1.26 BTU* per hour With a 12-inch wall of the same type of brick and 1 inch of insulating material such as Celotex and the same conditions as above, the heat transmission would be 1.60 BTU per hour but, with a wall 18 inches thick with 1 inch of insulation the heat transmission would be 1.30 BTU per hour There are obvious advantages in thinner walls if the insulation is equally good, not the least of these is that they are dryer

[illegible]

bricks are poorly burnt and the mortar is of lime and sand, with too great a proportion of sand

The best roofing from the point of view of heat deflection, is thatch, the thicker the better, but it has certain disadvantages, in that it makes an excellent harbourage for rats, birds, snakes, and insects of many kinds and it is easily fired and has to be repaired very frequently Rats and birds can be kept out by suitable wire netting

Pitched roofs are usually of tiles, a composition asbestos material, or galvanized iron, and flat roofs are of brick and concrete The galvanized iron roof which is cheap and serviceable is not as hot as one would imagine, provided it is painted white and there is a false roof of Celotex, or some other efficient insulating material, to intercept the radiated heat Celotex is also used in conjunction with concrete, but brick rubble on top of concrete is also very efficient

A pitched one-inch tile roof with a plastered ceiling has a transmission [illegible] at of a two inch [illegible] concrete roof is [illegible] ich insulation is [illegible] a transmission [illegible] and with 1 inch [illegible] concrete under [illegible] 337 BTU

A pitched roof should overhang the walls of the building by at least [illegible]

rays of the sun

The roofing material that has been introduced by Crowden referred to above, consists of three layers, the important layer being the centre one, this consists of a quarter of an inch of thickness of some composition material, the actual nature of which is not important, covered on either [illegible]

swords into plough-shares and our aeroplane scrap into aluminium foil, it may find a wider application The coefficient of transmission of this

* BTU = British thermal units

roofing is in the neighbourhood of 0 23 BTU per hour per square foot for each degree of difference of temperature between the inside and outside temperatures

Floors should be of finished concrete, terrazza or one of the new materials which are so attractive and, having a smooth finish, take a high polish All the corners, and the angles between the walls and the floor should be rounded to permit easy cleaning

Ground floors should be at least 18 inches above the ground, and there should be sufficient grated openings on all sides to provide cross-ventilation for the space below the floor

The ventilation space below the floor has the disadvantage of forming a harbourage for reptiles, rodents, and other animals, and it is a continual source of expense to keep the grating or wiring in a proper state of repair For this reason a solid plinth is favoured in some places, this must be covered by good concrete to prevent the damp rising up into the house

Ceilings s
extremely higl
room or hous
A ceiling of 9
of the room
conditioning

Windows should be of the casement type, and, if no shutters are provided, should swing outwards It is a great mistake to have windows too small They should be 2½ feet wide and 5 feet high, but, even more

Good wooden shutters with fixed slats are a great help in keeping down the temperature of the room, and can be used with the glass windows open or closed, according to whether the air is to be shut out or free ventilation encouraged

Doors should be wide, outside doors should have lintels and also be placed to assist cross-ventilation

Screening of doors and windows should be done in all malarious countries, whether other anti-malarial measures are adopted or not The old belief that screening raises the temperature of the room considerably is not borne out by the observations made by many investigators, though it does diminish air circulation In the Punjab, rented flats must be screened by the landlords, as are government bungalows The wire-netting should not be coarser than 16 meshes to the inch in order to exclude mosquitoes (*see* also **Malaria**).

The **verandahs** should be at least 12 feet wide and of sufficient length to be comfortable, there is a great advantage, in a country bungalow where space is unimportant, in having a verandah all round the house to protect the room walls from the sun, but in a town where space is necessarily limited, when the verandah is to be occupied much during the day, it should face east or north

The **aspect** of the house is an important point, but no hard-and fast rule can be laid down The full range of local seasonal conditions must be considered In Calcutta, for example, the prevailing wind in the hot

weather is from the south, in the cool weather when the wind may be too cold it is usually from the north, and storms usually come from the north west so that, despite the disadvantage of the hot sun during the middle of the day, the south is the aspect of choice

The rooms should be of good size, at least 15 feet square or its equivalent For country bungalows much larger rooms are the rule and are to be recommended provided air conditioning is not to be installed, but, if it is, there is a great advantage in a small room, which will usually be sufficient for ordinary living rooms or bedrooms when properly arranged. For example, wardrobes and cupboards (almirahs) are unsightly and are favourite nesting places of mice etc Built-in cupboards are more convenient and save space the old claim that they are damp is not applicable to modern building construction and has been found to be untrue in many tropical countries

The kitchen, or cook-house, should have a considerable amount of

smell of cooking is
is no direct closed
he house, even when
ants are made to do
be very offensive—
in their quarters, this objection is largely removed

Bathroom and toilet —It is usual in the houses of sojourners in hot countries to have at least one bathroom attached to each bedroom, and, as in the hottest weather two or three baths are often taken during the day, it is worth while having the bathroom as large as possible, and fitted with a fixed bath and hand basin and a sufficient number of convenient shelves A shower and an electric fan are comfortable additions The floors should be made of polished concrete, which should extend 5 feet at least up the walls, the rest of the walls and the ceiling being painted

If the spaces under the basin and bath cannot be completely enclosed in concrete, or some other vermin proof material, it is better to have them altogether open as the space is always damp and therefore an ideal refuge for cockroaches centipedes, rats, or even snakes

It is usual to have a flush toilet pan or commode in the bathroom, it is a convenient arrangement where the ratio one bathroom per person can be maintained, but otherwise it has obvious objections

When there is no connected water supply and drainage, a commode with an enamel ware pan is usually used in India, but this necessitates the continuous services of a 'sweeper' which may not always be possible. The larger type of bucket latrine with an automatic ash sprinkling arrangement,

or simply a box of ashes and a shovel, has very great advantages over the shallow enamel-ware pan where service is irregular, and is popular in many tropical countries

For garden use, the bore-hole latrine with a light superstructure that can be moved biennially is very satisfactory in most soils, and has the advantage of being cheap (For 'rural water supplies and sanitation' *see* other sections)

ARTIFICIAL COOLING

In a dry climate, use should be made of the *khus-khus tatti* This is a screen of loosely woven coconut fibre that is hung across a doorway or over a window opening, it is kept continually saturated with water by some automatic feeding device or by hand with the help of a garden hose The dry air comes in contact with this damp screen and causes evaporation which absorbs the heat from inside the room This arrangement can be made more efficient by the use of a suction fan to draw the air through the screen It is a surprising fact that this does not tend to make the atmosphere of an occupied room moister than when it is just closed up in the ordinary way, but it makes it a number of degrees cooler

Air-conditioning in offices and houses—Twenty-two years ago when the School of Tropical Medicine was opened in Calcutta, one of the largest cities in the tropics, our 'cool' room was one of our most popular exhibits It was an extravagance that was only justified by the fact that a large freezing plant had to be maintained for storing and preserving sera, etc, and that the cool room was necessary for certain chemical and bacteriological experiments Its existence was dependent on the foresight of Sir John Megaw, who seven years earlier, before the 1914 war, had seen the necessity for, and designed, this room, and it was appropriate that he, the first director of the School, should be the one to make the most use of it Gloomy prophets foretold that the users would be victims of all the worst ills that, in a tropical country, chilling is popularly supposed to generate, quite forgetting that in temperate and cold countries people are subjected to many-fold greater temperature changes every time they enter or leave their heated houses or rooms These ill-forebodings did not materialize, and today our prize exhibit of 1920 is of little interest to visitors of 1942, many of whom have similar installations in their offices and houses, and we are compelled to stress the historical interest as an excuse for showing it at all

[illegible] and, had

[illegible] ol, quiet
[illegible] lvantages
[illegible] nd other
flying insects with a high nuisance value are excluded, [illegible] the light can be shut out far more effectively than when one has to rely on open windows and doors for ventilation

The principle of the cool room at the School is a very simple one, air is driven over frozen pipes and conveyed by an *insulated shaft to inlet holes* near the roof on one side of the room, and on the other are a number of openings connected with an exit shaft The cool and dry air (dried by the precipitation of the moisture when it is cooled) falls in a cascade into the room and lifts the warm air which passes out by the air-exit shaft The walls of the room are lined with an insulating material and covered by glazed tiles, the windows are

double and the door is a thick one with rubber bands to ensure hermetical sealing these latter refinements undoubtedly added to the efficiency of the room but time has shown that they were unnecessary elaborations for the range of temperature that is required

Today air conditioning is altogether a much simpler affair single units are available that can be fitted into any window—in a matter of few minutes if the window is of the sash variety, and after some adjustment if it is a casement window If the windows and doors are reasonably close fitting no special measures need be taken but, when the building is an old one the openings that will usually be found around the doors can easily be filled with felt and, if a curtain is hung over the door there will be very little interchange of air whenever the door is opened

The domestic units are designed to cool rooms of different cubic capacities a machine of about one horse power will usually cool a room of 4 000 cubic feet very efficiently When the room has a very high ceiling [illegible]

with the same *floor space*

For air conditioning the best room is one with a north aspect (in the [illegible]

ape and if the
re that the air
only, that is
e smoke laden

or otherwise obnoxious an exhaust fan may be advisable, if this is not [illegible]

possible in it, as, until every object in the room has been cooled to the air temperature every surface is giving off heat that has to be absorbed

The cost of domestic air conditioning units is not prohibitive before the present war a machine sufficient to cool a moderate sized room of about 3 000 cubic feet cost about £100*, and, where reasonably priced power' electric current is available about a penny an hour to run For the average tropical sojourner this is not a high price to pay for the very great benefits to health and efficiency that it provides or, to put it another way, it is better value to have a good night's rest than an extra whiskey and soda

For those who can afford slightly larger plants and are prepared to make structural alterations in their houses, it is possible to air condition three or four rooms in a house at a cost equal to that of

* This was the price of a ¾ 'ton' (= ¾ horse power) machine delivered in Calcutta In the United States the price was about half this figure

two individual plants, especially if all the rooms are not likely to be used at the same time

Commercial houses that have introduced air-conditioning into their city offices have taken this step not as a luxury for their staff but as a sound business proposition

The temperature that it will be possible to provide in an air-conditioned room will naturally depend both on the machine and on the temperature and humidity outside The comfort zone in a tropical country, where one is wearing thin clothes, is between 72° and 78°F with the humidity at 60 per cent, which correspond to 68 5° and 73 5° effective temperatures, respectively, and most efficient air-conditioning plants will usually achieve the latter temperature and humidity even in the most unfavourable weather, but even a temperature of 80°F with this degree of humidity (effective temperature 75°) will be sufficiently low to ensure a good night's rest for most people

Most one-room plants will bring the temperature down to very near the minimum level within an hour, and the more powerful house plants, when they are turned on to one room, in a matter of a few minutes, so that it is not necessary to run a plant continuously

nurseries, etc , are being extensively air-conditioned in some countries, but [illegible] operating theatres Complete air- [illegible] desirable even in temperate countries [illegible] modern anæsthetic gases and for other [illegible] comfort of the operating personnel, to increase their efficiency, and to reduce the chances of sepsis, it is almost a necessity

There is still much to be learnt about the patient's temperature requirements before, during and after operation, but some data, especially with reference to fatalities, have been collected, and, although it is clear [illegible] for the operator are not identical with [illegible] reached in [illegible] °F in warm

In 1940, as a result of extensive experiments in the United States, one hospital was rebuilt with the operating theatres completely air-conditioned, by means of two separate air-conditioning systems One system serves all operating theatres using 100 per cent fresh air which is passed through disinfecting filters before being delivered into the room, [illegible] room, takes [illegible] the excess [illegible] 6 per cent [illegible] ess needed, [illegible] t upon the

DISEASES DUE TO THE DIRECT EFFECTS OF A TROPICAL CLIMATE

Introduction.—When in extreme climatic conditions, other environmental conditions being optimal, the compensatory mechanisms of the *healthy body fail to maintain the body within* the normal physiological limits, climate may be considered to be the *sole* factor in the production of

Under this heading only pathological conditions that are *solely* or *mainly* due to climatic conditions will be included, but it must be remembered that other factors, *e g* a specific infection, may influence the symptomatology to a greater or lesser degree, and it will be convenient to consider also in this chapter conditions of multiple ætiology that are sometimes attributed to the climate

PATHOLOGICAL CONDITIONS PRODUCED BY THE HEAT RAYS OF THE SUN

The following clinical conditions are recognized as being produced by heat —

A *Heat stroke*

(i) *Heat hyperpyrexia*

(ii) *Heat shock*

B *Heat exhaustion*

C *Heat cramps*

It would perhaps be appropriate to make some remark about the term 'sunstroke' which was commonly used until recently and which still causes a considerable amount of confusion, not only in the lay mind but amongst less well-informed medical personnel The term was introduced when it was thought that the solar spectrum contained some mysterious ray, usually attributed to the ultra-violet end of the spectrum, that had a direct and detrimental effect on nerve tissue There is no evidence for the existence of such a ray

Another objection to the term is the fact that *coup de soleil* (literally 'stroke of the sun') has already been claimed by the French, for quite a different condition namely for what we know as solar dermatitis It has been shown that the clinical conditions indicated by the term 'sunstroke' are all produced by heat effect on the body as a whole, though *it is conceivable* that localized heat applied to the brain or spinal cord might produce parallel conditions

A *Heat Stroke*

Definitions—*Heat hyperpyrexia* may be defined as a condition in which, in
to keep th
is another
feature
term to in

Epidemiology

ny means confined
The heat stroke
and Singapore is

lower than it is in a heat wave in New York, during heat waves in American cities the deaths attributable to heat amount to thousands per week In the latter cities, the other environmental factors, both personal and general that is, the unsuitable clothes housing conditions, etc enhance the effects of the climate on an unacclimatized population Again, it is in the dry desert areas of North Africa Arabia, Iraq Iran and the North West Frontier of India that the condition is more frequently encountered than in the true tropics

Seasonal incidence—It is of course in the hottest months of the year that most cases occur, and army statistics in India show that all heat hyperpyrexia occurs between May and September, half the cases occurring in June

Sex race habitus and habits—Male adults form the bulk of the victims, mainly on account of the circumstances under which they have to work and live In the army in India British troops are more susceptible than Indians and in the former the incidence is highest during the first two years of service after this there is another peak in the incidence curve at about 11 years'
first two years is undoubtedly due
how to mitigate its effects and of
and the second rise to increasir
acquired bad habits *e g* alcoho
certainly a contributing factor

The pyknotic individual is probably more susceptible than the asthenic, and obesity increases susceptibility

Alcoholism and over-eating are detrimental The teetotaller is undoubtedly at a great advantage in extreme conditions of heat, and alcohol should never be taken during the day in hot weather

Other environmental factors—In addition to climate the other important environmental factors are unsuitable clothes, ill-ventilation and overcrowding (*e g* the historical 'black hole of Calcutta')

Ætiology

Physiology—It
heat balance (*see* p
body functions (100 c
increased by work (i
calories an hour) T
the cooler immediate
latent, that is, absor

e temperature rises above this
Above this temperature all
midity rises and the wet-bulb
temperature nears 98 4 F this means of heat loss is also reduced to *nil*, and eventually the body temperature must rise

Air movement and clothing are also important factors and can be considered together
air movement will
movement of air are
temperatures above
provided the air is c

usually increases total heat loss and clothes decrease it, but in extreme conditions of heat the reverse may be the case

temperature, humidity, and air movement, a single unit, the effective temperature, has been introduced (*see* p 8) An effective temperature of 97°F is about the upper limit of tolerance of the body, even naked and at rest

The following figures regarding the effect of different combinations of temperature, humidity, air movement, and work from various sources are worth quoting —

In still air at rest it is just possible to survive—
a temperature of 100°F when the humidity is 90 per cent
" , 120°F " " " " 40 , ,
, " 140°F , , " " 15 ,
In each case the effective temperature is about 97°F

The body temperature will show a definite rise when the subject is—
at rest in moving air, at 93°F wet-bulb temperature*
, , still , " 88°F " ,
doing moderate work in moving air, at 86°F wet-bulb temperature
or doing moderate work in still " " 78°F " ,

The adverse effect of hot winds in a desert area is shown by the observation that at 128°F it is not possible to survive long in a wind of 20 miles per hour, whereas if the wind increases to 58 miles per hour long survival would not be possible even at 117°F

Associated factors —Of the *predisposing* factors, infection, usually—but not necessarily—with some organism that in ordinary circumstances might produce only a mild febrile attack (*e g* influenza, dengue sandfly

this point might mean nothing more than that those who have had one attack are constitutionally ill-fitted to withstand high temperatures and are therefore likely to suffer again

From another point of view, infection and the taking of alcohol might be considered to be the *determining* or *precipitating* factors, both are potent factors in upsetting the finely-balanced heat regulating mechanism when it is working under the strain of adverse environmental conditions

The Pathological Processes associated with the Breakdown of Heat Regulation

A Hyperpyrexia —A slight temporary rise of temperature under
ext
wh
or
rise
sweating, and a vicious circle will be established When the temperature reaches 108°F neuroglobin is precipitated and irreversible changes in the brain and cord occur

* The discrepancy between these figures and those shown in figure 2 are dependent on the fact that the latter were based on patients subjected to artificial hyperthermy and that a different criterion for a definite rise in temperature has obviously been taken

B Circulatory failure (heat shock)—In the attempt to get rid of

concentration, so that eventually there is an increase in the vascular bed, a decrease in the blood volume, and an increase in the viscosity of the blood This will lead to a fall of blood pressure and circulatory failure The recovery from such a condition is complicated by paralysis of the vaso-constrictor mechanism an expression of the general heat regulating failure This circulatory failure is enhanced by the taking of alcohol and/or of a heavy meal, the latter causing splanchnic dilatation and a further increase in the vascular bed

C Electrolytic imbalance—There is a continuous loss of chlorides and fluids in the perspiration, this fluid loss is usually replaced by pure water It has been shown that the blood chlorides fall during the hot

yrexia There
acid Marsh

	Cold weather	Hot weather	Patients suffering from heat effects
Blood sodium chloride mg per 100 c cm	494 ± 38	466 ± 29	448 ± 52 (mean of 45 patients)
Plasma bicarbonate millimols per 100 c cm	2 78 ± 0 26	2 54 ± 0 18	As low as 0 61
Blood lactic acid mg per 100 c cm	24 ± 6	30 ± 9	As high as 100

A better indicatic ... obtained
from the urine Ever ... d
from a heavy cloud of ...)
to complete absence

Severe muscular cramps are a clinical manifestation of this condition (*vide infra*, Heat Cramp)

D ... most important factor in hyper-
the
of
me
blo
ma
prc
rea
possible

All these conditions are frequently produced in a single case of heat ill effects but at any one time there is usually emphasis on one particular process and the symptoms will vary accordingly

Morbid Anatomy

There is usually a marked post mortem rise in temperature, but this will occur in other con
of death from heat hyper
and this may also seem
seriously dehydrated

there may be a petechial rash There is hyperæmia of all the organs, and particularly of the meninges which in certain instances also show œdema The heart is stopped firmly contracted in systole, and the blood in the vessels is dark and viscid suggesting tar in appearance and consistency

have been described,
at such temperatures
dies

Symptomatology

The onset —When the patient is already under observation, the onset of the symptoms may be noted from the beginning, and if circumstances permit, the attack can usually be aborted On the other hand, it may

Early and prodromal symptoms —The patient who is working up to an attack of heat hyperpyrexia will have a flushed and cyanosed appearance, his conjunctivæ will be red and his pupils contracted, and his skin will be intensely hot and dry, he may be drowsy, or uncomfortable and restless, and he will complain of a severe headache, of a constriction of the chest, often of frequency of micturition, and sometimes of a watery diarrhœa and vomiting At this stage the pulse rate will be slightly increased and the temperature raised (but this may be due to the infection for which he is already under medical observation and it is mainly in such cases that the early symptoms will be observed)

Second stage —Nearly all the signs and symptoms of the early stage are increased, drowsiness or slight restlessness turn to marked hysterical excitement amounting to mania in many cases, the urine becomes scanty and if tested will show a distinct cloud of albumin, the pulse is now full and rapid and the respirations increased, and the temperature is beginning to mount rapidly The knee jerks may be lost at this stage

Final stage —This is very often the stage at which the patient is first seen He is unconscious and often delirious, he has a burning skin, a cyanosed face, suffused conjunctivæ, bounding pulse, stertorous breathing, and the temperature may be to 108°F or higher All reflexes are lost
Stokes
°F in

Heat shock.—The first sign of the effects of heat may be syncope, later to be followed by hyperpyrexia, on the other hand, syncope may be a phase of the general condition, or it may result from too vigorous treatment in the hyperpyrexial stage There is collapse, vomiting and dyspnœa, the pulse is feeble, the systolic blood pressure falls to 70 mm Hg or so, and the rectal temperature may be low, but quite often the temperature in the rectum still remains high

Diagnosis

— the fact that in the vast majority of
ne other condition as well, and it is
However, if on a hot day a patient
in unconscious with no obvious signs

of trauma vigorous treat
the collapse immediately
conditions the most impo
vigorous action is indi

Prevention

Some of the ways of mitigating the effect
above (*see* p 16 *et seq*)

The methods adopted will naturally de
circumstances For meeting any particular se
in the production of heat stroke should be

of work and almost always to modify the cl
to this last is the case of A R P workers wh
or rubber clothes and masks to protect the
Work in particular should be graded to mee
stances The soldier who is under training sh
in the heat of the day reduced in the hot w
an arrangement ir ...
the military auth
hot so that they
this time or if th
important part of
imposed on the raw recruit

This brings one to the matter of acclir
The general whose soldiers can fight in all c
great advantage in real warfare and in indu
has to be done under adverse conditions Mu
the hours of work in trying circumstances very
are reported to have arranged hot chambers
work for gradually lengthening periods fo
withstand high temperatures *before* they go
Africa The armies of the British Empire ar
being able to train many of their soldiers in h

In mines in which work has to be done
very hot miners are acclimatized gradually
cooler seams at first and then being transfe
also by having their output of work in the
been found that after long spells of leave re

During short periods of exposure to heat

suffering from shock—may not ask for water, and they must therefore not only be allowed as much water as possible but must be pressed to take it

The salt requirements will be from 10 to 20 grammes a day and more in special circumstances, this may be taken in the food or with the fluid
y essential to increase the
f sodium chloride to each
nakes an unpleasant drink
ablets of salt with each
during very hot weather
and should certainly not be taken during the day

When the question of salt intake is in doubt, the urine should be tested for chlorides, the urinary chlorides should not be allowed to fall below 0 5 per cent

Test for chlorides in the urine —The following simple test is a very useful one for the ward or clinical laboratory The reagents required are potassium chromate 20 per cent and silver nitrate 2 9 per cent The test is carried out as follows —

Ten drops of urine are taken in a test-tube and a drop or so of potassium chromate added The mixture is well shaken The silver nitrate solution is then added drop by drop the test-tube being well shaken after the addition of each drop At a certain point the solution will turn brown, and remain brown after shaking This is considered as the end point of the test

The same pipette held at the same angle, preferably vertically must be used for measuring the urine and the silver nitrate After it has been used for measuring the urine the pipette must be washed out first with distilled water and then with a small amount of silver nitrate The potassium chromate is only an indicator and need not be measured accurately

The calculation is made from the number of drops of silver nitrate added to 10 drops of urine *before* the colour changes to brown one drop representing 1 gramme of chlorides calculated as NaCl, per litre, that is if the 7th drop turns the solution brown the amount is 6 grammes per litre, or 0.6 per cent.

In a normal person, 8 to 10 drops will be added before the solution turns brown In a dehydrated and hypochloræmic patient the brown colour will sometimes appear after the first drop, indicating that there are practically no chlorides present in the urine

In every large hospital in a country where heat stroke is common, there should be an air-conditioned ward in which the temperature is kept within the comfort zone This is particularly important in connection with industrial concerns where the work may entail subjection to temperatures even higher than that of the already high atmospheric temperature Heat stroke subjects can then be admitted straight into such a ward and the lowering of their temperatures is considerably facilitated Further, hospital patients showing the first signs of the failure of the heat-regulation mechanism can be transferred to the air-conditioned ward

Much can be done in a hospital by keeping an intelligent watch on all febrile patients, and very frequently, even in the absence of an air-conditioned ward, it will be possible to abort the attack Careful watch should also be kept on the urine to be sure that it contains the normal quantity of chlorides, and, if it does not, the salt intake should be increased

In industrial concerns, the medical officer should see that the environmental conditions are improved as much as is practicable (*e g* by artificial ventilation), that the work of the new recruit is graded, that the health of the labour force is maintained at the highest level by other sanitary measures (*e g* anti-malarial), that the worker's nutritional requirements are adequately met, and that he is supplied with plenty of safe fluid throughout the day (*vide supra*)

Treatment

The patient must be removed by the fastest means possible to a hospital or at least to some cooler place If he is already in hospital he should be moved to an air-conditioned room—if there is one—or to the coolest place available

All the *physical* means possible must be brought into action to bring down the temperature but drugs must be avoided at this stage Hydrotherapy offers the best opportunities cold baths, cold wet sheets, and ice packs, when ice is available, must be used freely, a hand or electric fan should be used to aid the cooling Cool enemata and cool intravenous salines may also be employed, a note of warning regarding the former is necessary, because the rectum is the best temperature indicator from which one ascertains the point at which the cooling treatment is to be discontinued

Massage is of great value in both the hyperpyrexial and the collapse phases It is important to maintain the circulation in the former phase so that the cooled peripheral blood is conveyed rapidly to the internal organs, and in the latter, it will naturally form part of the treatment for shock

The life of the unconscious person with heat stroke will depend on the early reduction of temperature so no possible means of lowering the temperature should be neglected once, however the temperature has been reduced to 102°F in the rectum vigorous measures should be discontinued, and the patient left in bed covered by a sheet or a light blanket, but he must be carefully watched to see that, (*a*) his temperature does not rise again, and (*b*) that he does not collapse and pass into a state of heat shock It is by no means an uncommon experience for a patient—especially one whose heat-regulating mechanism has been upset by some infection—to see saw between hyperpyrexia and heat shock throughout the whole day, and when—as happened many times in Iraq in the writer's experience during the 1914–18 war—a number of patients in the hospital are doing this, the amount of work that falls on the staff may well be imagined

For intravenous use, alkaline saline (sodium chloride—90 grains, calcium chloride—4 grains and sodium bicarbonate—160 grains, to a pint of water) should be given at a temperature of 60°F this has the effect of lowering temperature, helping the circulation counteracting both the chloride loss and the acid increase, and combating dehydration, so that it helps to counteract all four pathological processes mentioned above Warm (room temperature) intravenous alkaline saline will also be valuable in the collapse phase

Drugs should be avoided as far as possible No antipyretics must be given, and other drugs strongly contra indicated are strychnine and atropine, the former because it will increase the neuro-muscular tonicity and exaggerate cramps, and the latter because it inhibits perspiration Of the stimulants, caffein, camphor and ether in oil, and coramine can be used, in that [illegible] cases of acute delirium chloral [illegible] ctum, phenobarbitone is the safest [illegible] and it may also be used for sleeples[illegible] ns of each) fail

In patients in whom the blood pressure is high and there are signs of congestive heart failure, venesection should be considered, and, in unconscious cases with signs of cerebral irritation lumbar or cisternal puncture

may be advisable In the former case, the blood should if possible be taken into citrate saline, so that if the state of the patient changes over to the collapse phase later, it could be returned to his circulation

In the shock phase, whether it is the initial state or has followed hyperpyrexia, treatment is very much the same as for any case of shock, but the danger of pushing the patient over to the hyperpyrexial phase must always be kept in mind, and all measures that are aimed at increasing body temperature must be applied with great caution The treatment will *include nursing in the horizontal position, massage, possibly hot-water* bottles, intravenous saline or 5 per cent glucose, and of drugs, cortin or the synthetic desoxycorticosterone acetate, pituitrin and adrenalin

Diet —If the patient is conscious, he should be made to take fluids freely by the mouth, with glucose and sodium bicarbonate, and, if there is any chloride deficiency in the urine, sodium chloride up to two ounces in the twenty-four hours, must be given The question of diet need not be considered for twenty-four hours and then a fluid diet should be given for a day or two before the patient is allowed to return gradually to his full diet

Convalescence —This will depend on the gravity of the attack, but in any case the patient should not be allowed to return immediately to the environment in which the attack occurred, or to full work He should, if possible, have a holiday in a cool and quiet place, live on a low diet, take no alcohol, and pay special attention to his personal hygiene including keeping his bowels well regulated If it is thought advisable for him to '., he should at first return but his hours of work, and, if he nount of work *done should be* graded

Prognosis and sequelæ —Prognosis will depend almost entirely on the rapidity and efficiency with which treatment is carried out Rogers reported 8 3 per cent of deaths in patients whose temperature did not rise above 107°F, but when the temperature rises above 107°F or the patient remains unconscious for more than three hours the prognosis is bad, and, even if he recovers, he may suffer from the permanent effects of damage to nerve tissue The factors that militate against recovery are previous hypertension, and the complication of some serious febrile infection, such as typhoid

Sequelæ include long periods of low fever, headaches, myocardial weakness, enfeebled intellect, and sometimes dementia, according to Rogers the last occurs in about 10 per cent of severe cases of heat stroke After an attack of heat stroke the subject is said to be much more liable subsequently to the effects of heat

B Heat Exhaustion

The epidemiology of this condition is naturally closely allied to that of heat stroke, but there are differences For example, women are more liable to suffer from heat exhaustion than from heat stroke, and indolence is almost as likely to cause it as work However, the male worker is also liable to heat exhaustion which is very often a prodromal stage of heat stroke, or it may be looked upon as a mild attack of heat stroke

The ætiology is virtually the same, but there is more often a psychological element in heat exhaustion

Some sojourners appear to suffer from a form of thermal instability, the defect in their heat regulation mechanism is probably congenital in

the majority, but in a few it appears to be acquired after some serious febrile affection such as typhoid or heat stroke

The **symptoms** include weakness and lassitude headache, dizziness diarrhœa and vomiting mild cramps and sleeplessness A rapid pulse low blood pressure, and low fever will probably be the only clinical findings Chlorides will usually be low and may be absent from the urine In the case of the worker the first evidence may be that he faints at his work

Some degree of anæmia will often be found and it must be looked upon as a contributory cause and due to some other ætiological factor possibly of dietetic origin

In the thermal instability form the patient s temperature will rise to 102°F or higher every year when the effective temperature goes beyond a point say 85° at which most people are uncomfortable but able to compensate it These patients are often diagnosed as enteric though they don t usually feel very ill and the writer has recently had a patient who was treated as enteric 5 times in 7 years Many children s temperatures will always rise two degrees or so in the middle of the day in the hot weather without there being any discoverable cause

Amongst patients with this condition there will be a good proportion of neurasthenics and malingerers but care must be taken that the genuine cases are not classed amongst these

Treatment of the milder cases consists in removal of the patient from the surroundings that caused the condition very careful investigation for some underlying disease regulation of the diet and fluid intake—not forgetting the salt requirements regulation of the bowels and finally the administration of some tonic mixture

In the more severe cases the treatment will approximate to that given for heat stroke

C *Heat Cramp* (or *Stoker s Cramp*)

The excuse for allowing this symptom of the general syndrome of h...

...mperature is below
...onnected with salt
...re the further loss

The cramps usually occur in the muscles that are mo t used They may start either during work or some hours after work has ceased As well as those of the fingers—especially the flexors—fore-arms arms and legs the muscles of the pelvic girdle and abdomen are sometimes affected The involuntary muscles are never affected

The muscle contracts to an iron like hardness and during the time of th...

spasm may be started by active movement by a knock or even by a cold draught playing on the skin over the muscle

There is not necessarily much diminution in the urinary output, but there may be complete absence of chlorides from the urine The blood changes include an increase of plasma protein, and of plasma potassium, phosphorus and calcium, and a *marked diminution in plasma sodium* There is also an increase in cell volume percentage

Prophylaxis has been discussed above The most important feature is the provision of saline drinks Ten grains to the pint makes a reasonably palatable drink, but this may not be sufficient The taking of three 10-grain tablets with each pint of water is an additional precaution that may well be observed

Treatment consists in giving copious saline draughts, and intravenous and rectal saline, if necessary In severe cases, it may be necessary to relieve the cramps by giving morphia, or whiffs of chloroform

The similarity of this condition to hyperventilation tetany has been pointed out recently, but it seems unnecessary to suggest that the physiological hyperventilation which occurs in a hot climate is likely to be the cause of the cramps when there is a much better explanation

Morbus Britannicus is an allied condition that was at one time common amongst British sailors It was due to loss of chlorides in perspiration and vomitus, it is usually, but not necessarily, associated with a hot climate It received its name from the fact that Scandinavian sailors who lived on salt meat seldom suffered from it, whereas it was common amongst British sailors who lived on fresh meat

The abdominal muscles are usually affected—because of the important part played by vomiting—and the condition often simulates an acute abdomen

PATHOLOGICAL CONDITIONS PRODUCED BY THE ULTRA-VIOLET AND LIGHT RAYS OF THE SUN

One of the main efl ... the conversion of the chole ... The pathological condit ... is doubtful if it could ever ...

Solar dermatitis—the French *coup de soleil*—*is a condition that is* actually produced by the ultra-violet rays though the other sun's rays probably play some part in sensitizing the skin to the effects of these rays After over-exposure to the sun's rays, the first effects will appear in about two hours and the maximum effects in about six hours At first there is erythema, then a hyperæmia of varying intensity up to a serious congestion with œdema which may be followed by blistering, there is in *any case a superficial necrosis of the epidermis*, which eventually separates, as in a burn of the first degree, leaving the deeper layers of the skin exposed to the risk of secondary infection The immediate inflammatory reaction may be a serious one causing severe pain locally, high fever, and toxæmia, even more serious results may follow secondary infection Thus, though the condition is usually treated lightly and often jocularly, a severe sun-burn may have a fatal result

The parts most likely to be affected are the uncovered areas of skin on which the sun's rays fall vertically, the upper part of the forehead, the nose, and the malar eminence, the back of the neck and shoulders, the backs of the hands and the dorsa of the feet, and the knees and the fronts of the thighs if the exposure was in the sitting posture *A single layer of clothes*, even a thin handkerchief, will usually give complete protection

Sun-burn is usually the effect of direct sunlight, but serious sun-burns will also result from the reflection from snow or desert sand, and on a dull day the same effect may be produced by reflection from the clouds, so that care should be taken not to leave a sensitive patient on the verandah on such a day In the case of snow-burn the lesions will be mainly on the neck, the chin and lower part of the face

In specially sensitive individuals an urticaria sometimes develops on areas exposed to the sun, the condition has been called 'urticaria solaris' Rays between 3 800 and 5,000 Å are thought to be responsible for this somewhat rare effect (Arnold, 1941)

Frequent exposure to the sun's rays will eventually lead to the deposition of pigment, which gives some protection to the skin during subsequent exposures Whilst the rays between 2 800 and 3,100 Å are the most potent in the production of erythema the longer, light rays are more active in the production of pigment Repeated irritation from over-exposure to the sun's rays will produce keratosis and a pre cancerous condition which may eventually develop into rodent ulcer or epithelioma conditions that are common amongst men of European descent living open-air lives, in Australia for example

The natural pigment of the dark-skinned races protects these subjects to a large extent from these effects, and amongst fair-skinned races the brunette is less susceptible than the blonde (*vide supra*) Certain sub stances sensitize the skin to the effects of the ultra-violet rays, for example,

Amongst drugs, the heavy metals that are used for injection, *e g* gold, and substances that have fluorescent properties *e g* dyes, such as trypaflavin, used in the treatment of brucella infections cause sensitization

Prevention does not present any great difficulties, a single layer of clothing even a silk handkerchief, for example, or a thin layer of any oil will protect the skin from sun-burn Ordinary yellow vaseline, or 2 per cent tannic acid and 10 per cent castor oil in spirit as a prophylactic paint, are quite as good as any of the more expensive preparations that are advertised Usually the main difficulty is to keep the application from being washed away by the sweat, or absent-mindedly wiped away when the face is mopped

The treatment of sun-burn is purely palliative, cold cream or calamine lotion are probably the best substances to apply The more serious lesions must be treated as burns, with 2 per cent tannic acid and 10 per cent silver nitrate spray, with the triple dyes, or with whatever is the treatment indicated by the distribution of the lesions

Light stroke or severe form of *sun-headache is a common* and sometimes serious syndrome amongst newcomers to the special environmental conditions that produce it In this case, it is in almost every instance the reflected light rays from snow, desert sand, bare baked earth, and water surfaces, rather than the direct ones that are mainly responsible

The symptoms produced are intense headache, vomiting, prostration and fever Much of the so-called 'sunstroke' of a few decades ago wa undoubtedly this condition and today the layman still attributes hi symptoms to failure to keep his
local effect on the retina is a
considerable and in extreme cas
is usually temporary and fron
complete recovery may be confidently expected

The direct and indirect glare from the tropical sun undoubtedly play a part in the production of **night-blindness,** though this condition is more often due to psychological causes Strong light breaks down the visual purple in the retina which is again formed with the aid of vitamin A When the diet is deficient ... Other eye *symptoms of vitamin-A d* ... r *yellowish* foam-like patches on the ... the cornea) and keratomalacia (softer ... icing conditions such as hookworm disease and malaria, also increase this tendency to night-blindness

Prevention consists in the wearing of suitable tinted glasses In the green tropics Calobar-D lenses are suitable for general use and it is a mistake to have glasses unnecessarily dark, as this leads to eye strain when objects have to be viewed accurately, but in desert areas much darker glasses may be necessary

Treatment consists in rest in a darkened room Phenobarbitone should be given to relieve the severe headache, and for the prevention and treat- ... with the addition of vitamin-A
icient in this vitamin, the fish-
vitamin proper, and red-palm
or pre-vitamin A) from which
Any associated anæmia should
be treated appropriately

OTHER CONDITIONS THAT ARE ATTRIBUTED TO TROPICAL CLIMATE

Tropical Anæmia

It is no ... is however
only during ... the tropics
invariably l ... d and that
the home-returning sojourner has ceased to drink nightly a glass of port wine—the hæmatinic value of which is incidentally more than questionable —to counteract this thinning as his ship enters temperate waters The hæmoglobin content of the blood of the healthy sojourner is higher than of people of his class in ... the reason for this
should be sought and w
dietetic deficiency Th
also certainly not lower

Tropical Neurasthenia

— ... one that has come into general
to it and certainly
Many practitioners
iongst their patients
and have labelled them tropical neurasthenia ... far as we know, no series of cases has been studied and no scientific data regarding the most commonly associated physical conditions or even the environment in which *tropical neurasthenia* most frequently occurs has been collected

The ætiological factors can be grouped under the following heads and if the author were compelled to assign the degrees of importance to these factors he would give the percentages as indicated below —

(a)	Physical—disease or fatigue	50 per cent
(b)	Heredity	20 „ „
(c)	Social and environmental conditions	15 „ „
(d)	Mental strain—overwork and over-responsibility	5 „ „
(e)	Alcoholism and drug addiction	5 „ „
(f)	Climate *per se*	5 „ „

(a) *Physical*—Under
the list The commonest
followed by a condition of
discomfort The patient n
often he has not

His attention becomes centred on his bowels and his diet, in his over-anxiety to rectify the bowel disorder, he often remains on a low fluid diet for long periods and this leads to specific malnutrition of the bowel wall, stasis, fermentation and dilatation a condition of dysfunction of the small intestine, which may or may not be associated with ulceration of the large gut, and anæmia

Unsuitable, indifferent and monotonous food served in depressing surroundings that is liable to be the lot of the isolated bachelor will often result in loss of interest in food and the necessity to stimulate this by alcohol, this sequence again will lead to a state of undernourishment

Debilitating febrile conditions, such as malaria, also predispose to neurasthenia, especially when frequent relapses occur, and both dengue and sandfly fever are particularly liable to lead to a state of depression and mel ... d in suicide Finally, ... emetine, in the forr ... tors in producing ... drug after the cinchona alkaloids, in tropical practice, but it is certainly the most abused

A phase that follows a run of ill-health is the patient's fear of being ill again and this may be accompanied by worry that he is not doing his work and earning his pay, or, more egotistically, that he will lose his appointment This phase is usually much more highly developed in the married man with children

Fatigue may result from physical overwork, or the mistaken idea that exercise is the cure for all ills

(b) The influence of *heredity* will not be avoided by sending the patient abroad, as the heads of families—ill-advisedly encouraged by their family doctors—sometimes appear to think, or perhaps only hope This expedient often presents an easy way of getting rid of a grown-up 'problem child'. Or, the weaker type of man hopes to escape from the speed, bustle, and competition of life in the west by coming out to the

tropics, where, however, he finds that other qualities, *which also quite* frequently he lacks, are necessary, and again he has to face the fact that he is a failure *

Medical men who pass recruits for the tropics should pay particular attention to this aspect of their examination

(c) A young man comes out directly *from school or college—this* applies to both sojourners and educated natives of the country—and finds himself in some isolated spot many miles from the nearest potential [illegible]

On the other hand if he is happily married and has children, he has their illnesses and that of his wife to worry about as well as his own Finally, unhappy marriages are a very common cause of neurasthenia in either or in both partners

(d) *Mental strain* is a common cause of neurasthenia in any climate However, in the tropics, young and/or inexperienced sojourners are more *often suddenly thrust into positions of considerable responsibility, or of* special danger, for which they are not really fitted, and the experience is sometimes too much for them

(e) *Alcoholism* is probably more often a manifestation, or rather a [illegible] unstable [illegible] physical, [illegible] this sub- [illegible] he victim in a neurasthenic condition

Drug addiction is not common in sojourners, but cannot be excluded as a cause of neurasthenia

(f) Probably the only direct effect *of climate per se* in this capacit', except in very extreme conditions, is by interfering with rest at night

[illegible] nia are naturally different in men [illegible] s an even more important part, [illegible] or separations from children are also more prominent factors, and sexual neuroses are probably more common in women

Actual fear of servants, native *neighbours, snakes, insects, etc, is* probably a factor more or less confined to women Idleness and boredom replace overwork as factors Alcoholism is probably less common amongst women but cannot be excluded, and is to some extent replaced by 'chain smoking'

Symptoms—These do not differ materially from those exhibited in a temperate climate, and will vary with the ætiology Headaches, sleeplessness, inability to concentrate and loss of memory, indecision—even in such an unimportant matter as to whether to use a spoon or a fork—loss of

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* On this subject, Professor Culpin (1939) says 'there is a selective tendency at work by which home-misfits vainly seek a new environment for their mal-adjusted personalities'

emotional stability, hypochondriasis, and acute depression—even to the extent of committing or attempting suicide—are some of the common symptoms Frequently there will be tachycardia, a subnormal or an unstable temperature (*i e* one permanently raised about a degree above normal in the hot seasons), a blood pressure on the low side, and sweating of the palms Reflexes may be exaggerated

Treatment There is no specific line of treatment, and perhaps more

A sympathetic appreciation of all the patient's symptoms is essential but care should be taken not to be too mysterious about these, or he may suspect that he is suffering from some serious condition which is being hidden from him

Hypochondriasis often merges into neurasthenia and it is sometimes *a good plan to send a patient to some medical institution for a* 'thorough investigation' This will have a double effect, some unsuspected underlying cause, *e g* a protozoal or helminthic infection, gastric dysfunction or gall bladder infection, nasal sinuses, tonsils or teeth infection, an error of refraction, or even some easily corrected blood dyscrasia may be found, or, if nothing is discovered as a result of various investigations, the patient's confidence in his own health may be restored Naturally, whenever possible, these investigations should be carried out by the doctor himself, capital should be made out of any discovery however trivial and very thorough treatment given in the case of any important finding

The insomnia should be tackled first by investigating the environmental

Drugs will usually be necessary and should be given in such a form that the dose cannot be gauged accurately by the patient, that is, either in mixture or in cachet form A large and effective dose should be given at first and, when the habit of sleeping is acquired, the dose can be reduced.

R Chloral hydratis ..	gr xv	Spiritus ammonii aromatici	ʒss
Potassii bromidi Ammonii bromidi . Sodii bromidi	} aa gr x	Syrupi aurantii	ʒi
		Aquam chloroformi	ad ʒi

To be taken at bedtime, with a dose put ready to be taken 2 to 3 hours later if necessary

Phenobarbitone gr ii and paraldehyde ʒii are alternatives. Later, the chloral hydrate in the bromide mixture can be replaced by aspirin gr x, and this sleeping draught continued for some time.

If no cause for the headache can be found, APC powder (aspirin gr x, phenacetin gr iii and caffeine gr ii), Veganin, or Saridon should be tried first, and if these fail stronger drugs such as phenobarbitone may have to be used

Whilst sedatives are usually indicated at first, later, when the insomnia is under control and there is some general improvement in the mental condition, tonic mixtures should be prescribed Some of the proprietary mixtures, *e g* metatone, are useful in this connection

A change of environment to a cooler climate is the obvious treatment for a neurasthenic, but this measure should not be resorted to until some attempt has been made to cure or counteract the underlying cause, or causes If the patient is a sojourner and his home leave is due, he should certainly be sent home, but, if not, a month or two in a suitable hill station, or a short sea trip, preferably away from wife, or husband and or children, as the case is, may be sufficient, but care should be taken to choose a place where the patient will find suitable amusement and exercise, it is no help to a neurasthenic with dypsomaniacal tendencies to send him to a hill station to spend his time in the club bar !

Tropical Liver

This popular term describes a condition, probably commoner in the tropics than in temperate climates, that is not easy to define in medical terms

Heavy functional demands on the liver lead to a condition of hyperæmia, which is within physiological limits at first but later becomes a pathological congestion, as well as being a troublesome minor malady, the condition is of importance because it predisposes to hepatosis and liver abscess

[illegible] lead to [illegible] le, high- [illegible] id para- [illegible] is also [illegible] lominate [illegible] Up to a [illegible] roduced [illegible] alcoholic [illegible], in fact,

In the indigenous tropical resident, on the contrary, an excessive carbohydrate diet with a low-protein intake and vitamin deficiencies lead to a similar condition, and here again parasitic infections are very important

The main symptoms are headache dirty tongue, loss of appetite, general tiredness, sudden attacks of sleepiness, and a feeling of weight below the diaphragm There is usually some tenderness in the liver region and possibly slight enlargement, a general unhealthy coloration of the skin, and sometimes an icteric tint of the sclerotics

[illegible] adjustment of diet and habits, and an occa- [illegible] with sodium bicarbonate 3ii in a glass of [illegible] ing The regular taking of salts in the morning is a habit that is very easily acquired and is not a good one, as it is very liable to lead to constipation

Treatment should first be directed at the elimination of any parasitic infection As a general measure, after the diet has been adjusted, divided doses of calomel should be given at night, gr. ½ every half hour up to six doses, followed by salts in the morning, and then for a week a nightly pill·—

℞ Pilulae hydrargyri	..	gr iv
Extracti aloes	..	gr ii
Extracti hyoscyami siccati	..	gr i

... remark-

valuable alkaloid, but it is a very dangerous drug when it is abused.

... on after ... writer is ... How- ... to con-

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MALARIA

Introduction —Malaria is by far the most important disease in the realm of tropical medicine In the distant past it has caused the decay of empires, and in the near past the failure of the best conceived military campaigns, in our own times it has led to the abandonment of many engineering projects and has delayed innumerable others Of all diseases except possibly the common cold it is the most widespread, it is the cause of the greatest economic loss, and it has the highest incidence in nearly every tropical and sub-tropical country It has been subjected to a greater amount of study than any other tropical disease and a vast amount of knowledge has been accumulated about it, yet there are many *lacunæ* in this knowledge, it is the most easily treated of all serious diseases yet it is a disease in which the treatment is most often neglected, it is controllable and yet so seldom controlled, and it therefore still provides *the greatest problems to* the sanitarian and dominates the practice of the clinician in the tropics

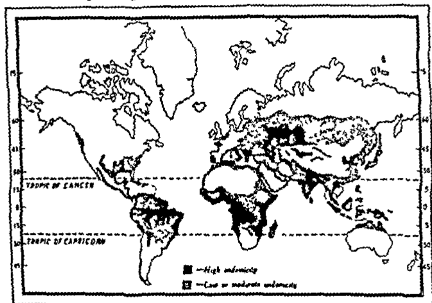
[illegible]

almost every country in the world, but mainly in the [illegible]
It is caused by a plasmodium, a protozoon of the order *Hæmosporidia*, which is transmitted from man to man by mosquitoes of the genus *Anopheles*

EPIDEMIOLOGY

Epidemiology means literally the science of epidemics, or it can be defined more liberally as the collection and the study of observed facts regarding the behaviour of disease in relation to man In the case of malaria, these *facts have been observed and the data regarding them* collected from the time of the historian Herodotus and probably earlier, and today are still being accumulated

Figure 4 Distribution of malaria throughout the world



Much of these data were collected *in total ignorance* of the cause of the disease and how it was transmitted from man to man, it was, however, the careful study of these accumulated facts that led, after journeys along many false trails, to the discovery of the true ætiology of malaria, and, conversely, it is our knowledge of this ætiology that has allowed us to explain many of the observed facts in its epidemiology, the reasons for which were hitherto obscure It is therefore logical first to summarize the epidemiological data, then to state what is known about the ætiology, and finally to attempt to correlate the two and explain, as far as our present knowledge goes, what are the factors that control the incidence of malaria

The data that have been accumulated can be arranged under a number of headings :—

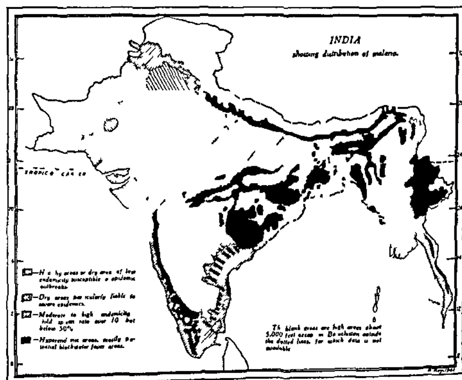
Geographical distribution.—This is world-wide, malaria occurs in the tropical, sub- [illegible] the former t [illegible] populated ter [illegible] at altitudes [illegible] which it has been reported (the incidence at high altitudes is probably a matter of temperature)—and that certain islands in the Pacific, *e g* Tahiti, Samoa, Fiji, Hawaii, are still free from the disease, the word 'still' is used deliberately, because at one time other islands, Reunion, Mauritius, and until quite recently Barbados, were reported to be free from malaria

Each of the malarial fevers caused by the four different species of parasite (v i) has a different distribution The widest is benign tertian whose domain extends from 60°N to 40°S *, quartan has a patchy distribution in all three zones, but malignant tertian is essentially a malaria of *warm countries, is limited by the 70°F* summer isotherm, and does not occur beyond 42°N The malaria caused by *Plasmodium ovale* has a sparse and patchy distribution as yet ill-defined

The world map shows that malaria occurs in almost every inhabited country on the
Canada and t
New Zealand,
always been

The distribution in India and Burma is shown in figure 5

Figure 5



In any country, district, or large area where
most always localities which are
ly, in countries in which malaria

* Beyond 45°N and 25°S it can scarcely be considered a disease of public health importance there is in fact not very much inhabited land as far south as 40°

is rare, there are localities which are intensely infected, even in a small town or village, there are often considerable differences in the malaria in different parts and one can go further and say that, in a single building, it may be found that those who live on the ground or lower floors are subject to malaria, whereas on the top floors the residents may be comparatively free It is thus essential, when studying malaria in any locality, to note carefully where the people live who are most subject to the disease

Observations of this kind were made in the earliest historical times. Herodotus (5th century B C) referred to the dangers to health of build-

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Seasonal incidence and variation from year to year—There are few places in which malaria occurs with equal intensity throughout the year Such variations are found even near the equator where, though there is little seasonal change in the temperature, other factors come into operation On the whole, however the seasonal variation in malaria is less marked the nearer one is to the equator The seasonal incidence also depends to some extent on the malaria species that is prevalent, and where more than one species is to be found in one place, which is usually the case, the malaria may be caused mainly by one species at one time of the year and another at another time (*see* figure 6) Malignant tertian malaria is often called æstivo-autumnal, for in many European countries it only occurs in the summer and autumn, and in all countries where there is a distinct cold season, the incidence of malignant tertian drops almost to zero during this season



Figure 6 In June, 80 per cent of the malaria is benign tertian, in October only 30 per cent of the malaria is benign tertian (Northern India)
(Acton H W, 1910)

Each country and even each district has its own seasonal malarial curve, in most places, this will show only minor variations from year to year, in its general shape, *even though the variations in the height of the curve may be considerable*

It is usual to consider malaria as endemic or epidemic, but, even in those localities in which it is endemic, the incidence of the disease is subject to periodical exacerbations. In the epidemic regions, the epidemic does not take the form of an introduction of malaria into a place where it did

not exist before—as is the case with cholera, for example—but of a sudden and often very dramatic flaring up of malaria in an area where it occurred in a mild form before, but was normally a disease of little public health importance during most of the year, in such an area, though the *individual* conditions that affect malarial incidence may not vary much from year to year, it is the concatenation of a number of events that brings about a state of affairs favourable for an epidemic, *cf* Sydenham's epidemic constitution Epidemics tend to occur in cycles of a definite number of years

In India there are two main types of malaria seasonal curve the Punjab type and the Bengal-Assam type In the former, the incidence is low during most of the year and with the onset of the rains there *is a sudden rise which will in certain years amount to an epidemic* These epidemics have been studied by the health authorities and it has been shown that it is often possible to foretell whether it will be a normal or bad year for malaria This information is very valuable because it enables these authorities to set in motion the special organization for dealing with the epidemic immediately it arises In the endemic areas, *e g* in Assam and Bengal, the disease is perennial, but the curve shows a steady rise in July and August and reaches its peak in about November, after which it falls fairly rapidly

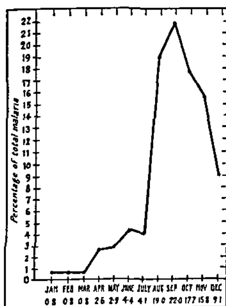


Figure 7 Seasonal malaria curve in Delhi

(Knowles and White 1930)

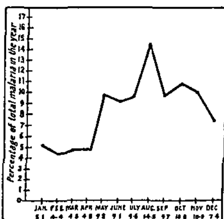


Figure 8 Seasonal malaria curve in the Assam Valley

(Knowles and White 1930)

A minor spring rise in the incidence curve has often been noticed, particularly in benign tertian areas in Europe

These endemic areas are not entirely immune from epidemics, as was shown recently by the Ceylon epidemic of 1934/1935

In studying malaria in a locality an attempt should be made to prepare a seasonal graph from past records if they are available or ... If possible the malaria caused by ... plotted separately The larger the the better, and *if only one year, or*

a small number of years, are included, an attempt should be made by careful local enquiry to ascertain if the year or years were 'normal' as far as malaria was concerned

Age and sex incidence —Individuals of all ages are subject to malaria There have been a number of instances of congenital infection reported, but this is not a normal mode of transmission of the disease it will be referred to again later Children are particularly liable to infection, and in them it usually takes a serious form In a malaria-infected community, children are important for two reasons, firstly, they react to malarial

of the disease

The age composition of a community is thus an important factor in normal epidemiology If children form a large proportion of the population malaria will be more difficult to control

Race and caste —Persons of all races seem to be equally susceptible to infection, provided the circumstances in which they live are the same, though there are considerable i The morbidity caused by malaria d there are many instances in which tl appear to be unaffected by the disease, whereas foreigners, of whatever race, become seriously ill when infected, one of the best examples of this is provided by blackwater fever, a malarial disease (*vide infra*) It has also frequently been observed that any disturbance of the population, for example, the migration of a large number of persons into another country, may not only lead to a high incidence of malaria amongst the immigrants but also to a great exacerbation of the disease amongst the indigenous inhabitants This is a recognized principle of herd immunity that is certainly applicable to malaria

The racial composition of a population and more especially any changes that have taken place recently are therefore important facts to be noted

infected, who has to make long marches in trying circumstances is very liable to suffer from malaria, either an initial attack or a relapse Any severe physical strain or trauma, *e g* surgical or obstetric operations, *x* ray applications to the spleen, or sudden cold, may precipitate an attack in an infected subject

The economic factor is one of great importance in determining the development of immunity to malaria It has been shown frequently that when the

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epidemics

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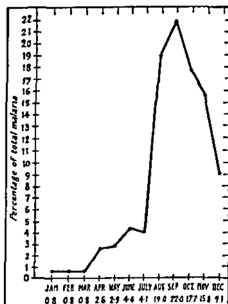


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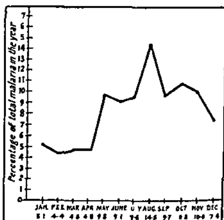


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Race and caste—Persons of all races seem to be equally susceptible to infection provided the circumstances in which they live are the same, though there are considerable individual variations in susceptibility The morbidity caused by malaria does, however, vary considerably, and there are many instances in which the members of the indigenous races appear to be unaffected by the disease, whereas foreigners of whatever race, become seriously ill when infected, one of the best examples of this is provided by blackwater fever, a malarial disease (*vide infra*) It has also frequently been observed that any disturbance of the population, for example, the migration of a large number of persons into another country, may not only lead to a high incidence of malaria amongst the immigrants but also to a great exacerbation of the disease amongst the indigenous inhabitants This is a recognized principle of herd immunity that is certainly applicable to malaria

The racial composition of a population and more especially any changes that have taken place recently are therefore important facts to be noted

Occupation habits and economic status—Numerous observations have been made under this heading, back to the time of the Roman historians who pointed out that in certain malarious districts it was dangerous to walk out at night and loiter by the water's edge The danger to soldiers carrying out night operations or standing guard at night, and to police on night duty has frequently been observed Again the soldier previously infected, who has to make long marches in trying circumstances is very liable to suffer from malaria either an initial attack or a relapse Any severe physical strain or trauma *e g* surgical or obstetric operations *x* ray applications to the spleen, or sudden cold, may precipitate an attack in an infected subject

The economic factor is one of great importance in determining the development of immunity to malaria It has been shown frequently that when the economic condition of a rural population in particular, improves the malaria loses much of its morbid potentialities Conversely, severe epidemics have often been correlated with an economic depression

The best example is the Roman Campagna which once harbouring a flourishing agricultural community, was through misgovernment allowed *to degenerate* at intervals into a deadly malarious swamp for nearly two thousand years, but has now reacquired its former agricultural *prosperity* and malaria h[illegible] * Other examples of how *development* [illegible] ia are the fen districts in England the [illegible] many Lower Egypt and in India the deltas of the Cauvery and the Godavari Conversely Corsica is often quoted as a country in which agricultural deterioration has led to a great increase of malaria, and the Ceylon epidemic followed a period of economic depression

It is thus obviously important to collect full data under all these headings

ÆTIOLOGY

Historical —The early theories regarding the cause of malaria were numerous The word 'mal-aria (bad air) is evidence of one of the earlier theories not unreasonably founded on the fact that the disease prevailed in low marshy country where the poisonous miasma arose from the ground at night Another theory was connected with water and it has been suggested that the first Roman aqueducts were built on account of the prevalence of fever in Rome the partial success of this measure would be accounted for by the reduction of other water borne fevers

Night flying biting insects came under suspicion very frequently and Herodotus referred to the use of what we should call mosquito nets by the Egyptians

Laveran described the malaria parasite in 1880 this discovery was developed considerably by the Italian workers Marchiafava Celli and Golgi who demon strated the different species and associated these with the various clinical pictures This work was hampered by the absence of a suitable stain for the parasites and the perfection of a staining technique by Romanowsky in 1891 considerably aided future investigations

This discovery of the causal organism opened up the field for the investigation into the mode of transmission of this parasite from man to man It is difficult to trace the germ of an idea to its origin Credit is due to the Jules Vernes and H G Wellses of medical science who produce many excellent and also it should be remembered many false ideas It is however the man who has the perspicacity to sort the grain from the chaff (or who the cynics will say is lucky enough to follow the right trail) and develops the ideas that usually gets and probably deserves the most credit When Manson first turned his attention to the problem of the transmission of malaria the idea of an arthropod carrying a disease was new but not entirely new for as back as 1869 Fedtschenko sug gested that dracontiasis was transmitted through the medium of cyclops (an

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*— [illegible] t be questioned It has been [illegible] causes malaria whilst at the [illegible] uses poverty with its sequel

Hackett (1937) has questioned whether malnutrition does cause malaria and adopts the view that the reaction is all in one direction namely malaria causing poverty and malnutrition This view is supported by Covell (private communi cations)

In support of this view, these very widely experienced malariologists quote much suggestive data including the fact that the healthy and well fed British soldier is very susceptible to malaria which in him quite often takes a fatal course

This and most of the other examples they quote do not in any way run counter to the views of the writer regarding malnutrition and malaria he believes from medical and pathological as well as from epidemiological experience that nutrition affects not the non immune patient's immediate response to a malarial attack but rather the way that immunity develops in the individual subjected to repeated attacks of malaria

observation subsequently shown to be correct) Ten years later, Manson discovered filarial embryos in the mosquito, and from this time onwards he probably nursed the idea that malaria was also in some way connected with the mosquito In 1883 King in America published a paper containing a well-reasoned justification for the mosquito hypothesis Manson interested Ronald Ross in this subject and in 1897, working in Secunderabad Ross discovered the pigmented bodies (oöcysts) in the stomach wall of the dapple-winged (anopheles) mosquito

The causal organism —This is a protozoal parasite of the class Sporozoa the order Hæmosporidia, and the genus *Plasmodium* There are four recognized* species of *Plasmodium* that infect man in nature, *Plasmodium falciparum*
that causes quartan m
P ovale that causes a
malaria parasite, P kn
causes transient malaria, but it is doubtful if this occurs in nature)

There are undoubtedly a large number of 'strains' of parasites of

induced by infection with the Madagascar strain, and the Rome strain of malignant tertian is particularly resistant to treatment

In one locality there are probably many strains, this is indicated by the fact that, in a very malarious place, it may be many years before the children acquire immunity to all the malarial strains in the locality

The life cycles of the four species of human plasmodium are practically the same

There are two phases in the life of the malaria parasite, an intracorporeal phase in the intermediate host—man, and an extra-corporeal phase in the definitive host—the female mosquito, and two cycles, the asexual and the sexual These phases and cycles do not correspond with each other

The forms of the malaria parasite that are found in man —The ring form, which is seen in a Romanowsky-stained film as a pale blue disc with a red chromatin dot at the edge lying within a red blood corpuscle, is at first very small but rapidly
dark pigment (hæmozoin),
fills practically the whole
cytoplasm, its chromatin is
into masses, the fragments
in size now tend to become arranged evenly throughout the cytoplasm and

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P vivax from 14 to 24 and in *P falciparum* the number is more variable, from 12 to 32 The *merozoites then attach themselves to and eventually* enter red cells where they again start the asexual cycle or they may develop into sexual forms, the male and the female gametocytes The fully developed gametocyte fills the whole cell like the schizont, but the gametocytes of the three malaria species have distinctive characteristics The most distinctive is the crescent form of the malignant tertian parasite, the male gametocyte is long and slender with a large nucleus and the pigment scattered throughout the cytoplasm whereas the female is stouter and shorter, and has a small nucleus with the pigment distributed around it The *P vivax* tertian and *P malariæ* gametocytes are more or less globular in the former the nucleus is an irregular mass and in the latter it takes the form of a rod or band (Further details of the morphology of the different species will be given below, *see* DIAGNOSIS)

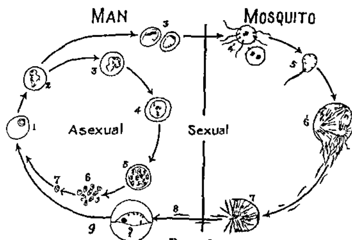


Figure 9

Asexual cycle

1 Ring form
2 Growing trophozoite
3 Trophozoite
4 Schizont
5 Fully grown schizont *rosette form*
6 Burst rosette
7 Merozoites

Sexual cycle

1 Ring form
2 Growing trophozoite
3 Gametocytes ♂ and ♀
4 Flagellate bodies and gametocyte ♀ } in mosquitoes
5 Fertilized gamete (Ookinete not shown) } in mosquitoes
6 Oocyst—in stomach wall } in mosquitoes
7 Sporozoites—in salivary gland } in mosquitoes
8 Free sporozoites
9 Exo-erythrocytic stage

The asexual cycle —The cycle—ring, schizont, rosette merozoite, and again ring—lasts 48 hours in malignant tertian and in benign tertian and 72 hours in quartan malaria This fact determines the periodicity of the fever the rigor corresponds to the bursting of the rosette This asexual

cycle leads to the multiplication of the parasites within the host, but, if it were the only form of development, there would be no chance of propagation of the species beyond this individual host, for the particular parasitic brood would end its existence in this host, they might kill him, or they might be destroyed by the cellular or humoral reactions of the host's tissues, therefore, for the continuance of the parasite's existence the sexual phase is necessary (*see* figure 9)

On the other hand the sexual parasites, the gametocytes, have no future within the individual host in which they are formed, for they are capable of no further development Their future lies only in the mosquito, and if they are not taken up by a suitable mosquito, after living for about three weeks in the blood of their host, they die

The sexual cycle —When a mosquito vector feeds on an infected man, it takes in a number of malaria parasites Any asexual forms will die, but the mature male and female gametocytes continue to develop in the stomach of the mosquito, from the male gametocyte a number of flagellate bodies separate and eventually enter a female gametocyte which they fertilize, the fertilized gametocyte, or gamete, undergoes development and becomes an ookinete an elongated body with considerable powers of penetration The ookinete penetrates the endothelial lining and buries itself in the wall of the mosquito's stomach where [illegible] These oocysts can be seen e [illegible] ound glistening bodies in the [illegible] are 40 to 80 μ in size The [illegible] r of sporozoites into the bo [illegible] are motile bodies and find their way into every part of the body of the mosquito except the ovaries but in the salivary glands they find a particularly suitable medium for continuing their existence Once the sporozoites have reached the salivary glands, whenever the mosquito takes a blood meal the sporozoites escape with the salivary material and enter the body of their new host

The time taken in this phase in the mosquito is variable, according to the conditions, the shortest time is probably about 8 days but under adverse conditions, particularly in the cold when the mosquito is hibernating it may take many months The average time in moderately favourable circumstances is usually looked upon as about 12 days

It was at one time thought that a certain minimum number of gametocytes had to be present in the blood before the mosquito would become infected, this number was placed at 12 by Darling (1909) Recent work has shown that there are many other factors besides the number of gametocytes that determine infection of the mosquito, these include species and strain of plasmodium, and species and individual variability of mosquito, some individuals of recognized vector species being entirely refractory to infection

[illegible]

Development only takes place in the *female* mosquito

There is considerable uncertainty as to exactly what happens to the sporozoite when it enters man A few facts are known it does not for example, remain in the blood stream, for blood taken during the first eight days is not infective On analogy with observations made in birds it is thought that the parasite enters certain reticulo-endothelial cells of the host and there multiplies by schizogony After this latent period the malaria parasite reappears in the peripheral blood as a ring form, it then completes a number of asexual cycles and may again become a gametocyte

The term 'mosquito cycle' is sometimes used but actually there is no *cycle* in the mosquito The parasites enter the mosquito as gametocytes and leave it as sporozoites From a pair of gametocytes a very large n mber of sporozo't [illegible]

transmitting malaria for over 90 days The sexual *cycle* is only completed when gametocytes are again formed, thus both the mosquito and man are essential for this cycle to take place The average period of the sexual cycle is at least a month, this is made up by about 12 days' development in the mosquito about 12 days' incubation period in man, and say another six days from the time the infection reaches the clinical 'threshold' to the appearance of gametocytes, these figures are not minimal but probably represent a low average

The essentials for the natural transmission of malaria and the factors influencing them —

The essentials are —

A *The malaria parasite*

B *The mosquito vector*

C *Man*

D *The links between B and C, i e* the lines of communication along which the parasite travels

In the absence of any one of these essentials, malaria will not exist If the conditions influencing all these four essentials favour malariogenesis the incidence of malaria will be maximal if conditions influencing *any* of them are unfavourable malaria incidence will be sub maximal and if conditions influencing *all* of them are unfavourable malaria will be minimal, or may not occur

It is by the study of the various climatic and other terrestrial factors that influence these four essentials that we shall understand and explain the observed facts regarding the incidence, distribution etc, of malaria, which we have recorded and which we know as the epidemiology of the disease

This is not however an academic study for it is only by knowing what these malariogenic factors are and how they exert their influence that we can hope to eliminate reduce or avoid these influences The study of how this has been and is being done, how it can be done and how it might be done constitute the science of malariology even the essentials of which would fill a large volume here it is only possible to give the barest outline

The malariogenic factors are conveniently grouped under these four headings —

A *The malaria parasite* —As a very large proportion of the human race has been or is infected with some species of malaria parasite, it is very unlikely that a community exists where the other three essentials are present and yet there are no malaria parasites, such a state of affairs is conceivable (and has a parallel in another disease, *i e* yellow fever), and, as long as no infected man or mosquito was introduced, the community would remain free from malaria

However, apart from these theoretical considerations the parasite factor is an important one, and malaria in any locality will be influenced largely by the number and immunological variety of the strains of malaria parasite present Further it has been shown that other conditions remaining unchanged new strains of malaria parasite introduced into a community by immigration of foreigners importation of foreign labour, etc (*vide supra*), will cause a sharp rise in the incidence of malaria in that community

Again, the proximity of the reservoirs of malarial infection will be an important factor in determining the incidence in a locality

The parasite has two phases and the factors that influence it will be different in each case

In
the dev
mosquit
development only takes place up to the oocyst stage A temperature of 60°F and a humidity of 63 per cent (to ensure longevity of the mosquito) are necessary for the development of *P falciparum* this explains the absence of malignant tertian malaria from cold countries its autumn periodicity in temperate countries and in hot countries its disappearance during periods of very high temperature but low humidity

Other possibilities that have not yet been fully explored are the existence of other parasitic infections in the mosquito and the nature of its food, for mosquitoes take other fluids besides their blood meals

In *man*, the parasite is influenced by the host's natural and acquired immunity (*vide infra*)

Another factor is the formation of gametocytes It has been suggested that this is a phenomenon of immunity but this is quite obviously not the case for infants who enjoy the least immunity are the greatest gametocyte producers If therefore any correlation between gametocyte formation and immunity exists, it is a negative one

For transmission to occur there must be gametocytes in the peripheral blood, their presence, quantitatively considered, is therefore an important factor in malariogenesis

Finally, the effects of therapy have to be considered under this heading, any drug that destroys gametocytes directly or indirectly is capable of influencing malarial endemicity

B *The mosquito vector* —Not all mosquitoes carry malaria, only ce
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particular aspect of the science of malariology has now probably received more attention than any other, but knowledge on the differentiation of species is still incomplete, and apparently homogeneous species, *e g* *A maculipennis* in Europe, are frequently being shown to be made up of

In Europe	*A maculipennis* group *superpictus*, *sergenti* and *claviger*
India and Ceylon	*A culicifacies*, *philippinensis* group, *fluviatilis*, *minimus*, *superpictus*, *sundaicus* and *stephensi*.
Palestine and Syria	*A elutus* and *superpictus*
Iraq and Iran	*A elutus*, *superpictus* and *stephensi*.
China	*A minimus hyrcanus* and *maculipennis* group
Burma and Siam	*A minimus* and *sundaicus*
Malaya	*A maculatus*, *umbrosus*, *sundaicus*, *aconitus* and *hyrcanus*
Egypt	*A pharoensis*
Africa	*A gambiæ* and *funestus*
Australasia	*A punctulatus* group, *amictus* and *barbirostris*
America	*A quadrimaculatus*, *crucians*, *maculipennis*, *punctimacula* *pseudo-punctipennis*, *darlingi* *albimanus*, *albitarsis* and recently *gambiæ*

All potential vectors are not of importance as vectors in nature, nor are apparently identical species of equal importance as vectors in all localities in which they are found, *e g* *A subpictus* carries malaria in New Guinea, but, though the Bengal species can be infected in the laboratory, *in nature it is never found infected*, *apparently* because it is a delicate species and does not survive long

The life cycle of the mosquito —This is similar to that of all nematocera The adult mosquito or imago, lays its eggs on a water surface where they float (figure 10 1*a* and 1*b*) From the ovum a larva hatches out which feeds on algæ and other organic matter It also requires air, so that it has continually to come to the surface and normally rests just below the surface with its spiracles in contact with the air (figure 10 2*a* and 2*b*) The larva after several moults changes into a pupa (figure 10 3*a* and 3*b*) which does not require food Finally, from the pupa the imago, or adult mosquito (figure 10 4*a* and 4*b*), emerges Thus, for development of ovum to adult water is necessary

The adult mosquito lives on fruit and plant juices, but the female requires a blood meal for the matu ... he human or even mammalian blood ... are night feeders The di ... has been studied very fre ... species Normally the m ... its food Some species ar ... hundred yards or so from ... *Aedes ægypti*) However, and *it must be remembere* ... to fly back to their breeding place ... malaria-infected mosquitoes (*A gambiæ* or *A funestus*) being blown a distance of well over a mile from a malarious shore into a ship The normal range of malaria-carrying mosquitoes is under a mile

The time taken to complete the life cycle of the mosquito varies according to the conditions, and is mainly controlled by temperature Under optimum conditions development from ovum to imago may be ... this is probably exceptional ... ut a month even in summer, ... d may be arrested for many ... *va, or adult stages, according*

to the species Similarly, the length of life of the adult mosquito varies considerably, in cold climates where it undergoes periods of hibernation, it will live up to nine months, but in the tropics, where metabolism is speeded

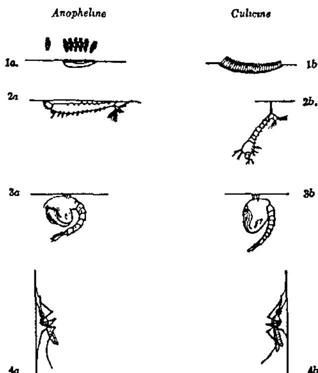


Figure 10

Anopheline	*Culicine*
1a Eggs with floats also shows how they float	1b Eggs and float
2a Larva floats horizontally on the water surface	2b Larva hanging from water surface
3a Pupa breathing trumpets funnel-shaped.	3b Pupa breathing trumpets long and narrow
4a Imago body straight	4b Imago hunch-backed

up, its average life span is probably less than a month In nature, the mosquito is subject to many adverse influences, infections, ecto-parasites, and innumerable natural enemies, fish in the water, bats in the air, and lizards on the wall, so, though it is extremely fertile, its life is a precarious one, this is an important factor and explains the relatively low sporozoite infection rate amongst mosquitoes caught in nature even in a highly malarious locality

With this complicated life cycle it will be obvious that the factors that influence the mosquito will be numerous, these include temperature, humidity, rainfall, sub-soil water level, the nature of the water, the nature of the soil, physiographical conditions, both natural and man-

made, altitude (mainly in its relation to temperature), *vegetation*, biological competition, and natural enemies

When these conditions are very unfavourable mosquitoes will be reduced to a minimum, or they may be absent altogether and malaria will not occur, but there are places where the conditions are extremely favour-

[illegible]

i vector species have
aused a considerable
is the introduction
y the trans-Atlantic
d a most disastrous
increase in malaria

It is impossible to summarize the effects of these various factors, or to make any dogmatic statements, such as, for example, that rainfall is *favourable to mosquitoes, for it may be just the reverse, and there are* many circumstances in which rainfall will actually stop malarial incidence, or that abundant vegetation favours the mosquito and malarial incidence, for there are some vector species that disappear when streams are shaded (*Anopheles minimus*), though others (*A umbrosus*) require shade, some mosquitoes flourish only in clear water, others are less particular and seem to prefer contaminated water, yet others need a degree of salinity (*A sundaicus*), some prefer stagnant pools, others running water, and so on It does not mean that, because this information cannot be summarized, our knowledge on these subjects is confused and unsatisfactory On the contrary, there is a very great deal of accurate and detailed information *on the habits of most of the important vector species It is a matter* of primary importance that anyone who has any responsibility in the matter of malaria control should find out first what are the local vector species and the relative importance of each, he should then ascertain from the numerous books and other *publications on malariology what are the habits* [illegible] and finally by observation he should find
m to their normal behaviour There are
species behaving differently in different
exclusively on man in the Wynaad and
potent vector, whereas in the Himalayan
foot-hills it feeds exclusively on cattle and is of practically no importance as a vector], but such instances are rare, and the instances in which *in nature* they have been made to change their habits (*e g* to breed in fresh water when they have been deprived of saline water) are even rarer It will usually be found that *one species only is of real importance* and this will *facilitate control* very considerably

C Man —The influence of the human factor in the determination of malarial incidence has been to some extent neglected since the day when attention was first attracted to the parasite and the mosquito

For all practical purposes, man is the only intermediate host of the malaria species with which we are now concerned, though in certain jungle areas a higher mosquito-infection rate than appears to be explainable on the grounds of the very sparse human population has led to the suggestion that apes may be the source of infection There are of course many other plasmodia besides the four 'human' species, and man has been infected with the monkey plasmodium, *P knowlesi*, under artificial conditions

The important factors under this heading are the density and age composition of the population, the previous malarial experience of the community as a whole or of the different groups that compose a community, the climatic conditions under which they live, their economic status and general mode of life, and their general state of health and nutrition

Man enjoys both natural and acquired immunity to malarial infection

[illegible]

man with malaria and there are the many instances when the malaria has not developed for some years, until the host has been subjected to cold or some physical strain and his natural resistance thereby lowered

There is as yet no agreement on the nature of acquired immunity There is little doubt that some, both cellular and humoral, immunity is [illegible] nity and to a much less [illegible] The other explanations [illegible] from malaria is that all [illegible] were killed off in their infancy, or that the apparent immunity is really a 'premunition', that is to say, the individual is already infected with malaria so that his body defences are active and prevent super-infection, which some might argue, constitutes immunity

[illegible]

high infection rate, though short of 100 per cent but the average number of parasites will be far less, amounting to perhaps one-hundredth that in the infants, and they will only suffer from occasional febrile attacks Christophers (1925) has shown that, under these conditions, the infection rate, the parasite count and the frequency of the febrile attacks show a steady decline as the age advances

There is however no doubt that this immunity is very labile and that when the general powers of resistance of the host are lowered for any reason, for example, by famine and hardships, as well as by fatigue and cold, mentioned above, he is far more susceptible to malarial morbidity, even if not to malaria infection

Conversely, when they are raised by good food and comfortable living conditions, he will be much less liable to malarial morbidity and probably to malaria infection

Thus, immunity is important to the individual, but even more important to the community, for the rise in immunity means a reduction in the circulating parasites and therefore in the source of infection to others Conversely, a bad general breakdown in immunity, from any cause, will lead to a vicious circle of increased infection and increased morbidity, sudden disastrous epidemics that sometimes occur even in endemic areas are explainable in this way

The presence of children in a community will increase incidence both on account of the heavy infections that they suffer as a result of their low immunity, and because they produce large numbers of gametocytes

The introduction of a number of non immunes—either non immune to all malaria strains or to the local strains—into a malarious community will be like adding fuel to a smouldering fire, and will increase malaria incidence in the whole community

D The links between man and the mosquito —Both man and the mosquito are essential but if they could be kept apart malaria would die out The stronger the links, the higher the malaria incidence, and *vice versa* The important factors can be considered under two headings, (i) general and (ii) local and personal

(i) The general factors include density of human population, density of mosquito vector population, living conditions of the population, and movements of the population, air movements and prevailing winds, and animal deviation (zoophilism)

This question of the densities of the human and mosquito populations and malaria incidence is a mathematical problem, but it is not an entirely simple one On the whole the denser the populations the greater are the chances of contact between man and the mosquito, but this would seem to suggest that the disease should be more prevalent in towns, whereas we know that it is not The reason for this is that in towns the density of the human population is more than counterbalanced by the sparsity of the mosquito population

Again it must be remembered that to transmit malaria the mosquito must take at least two human blood feeds, there are many factors which militate against the chance of this occurring for example, the high mortality amongst mosquitoes in nature, which means a short survival period for each individual mosquito this cannot be entirely compensated by a higher propagation rate which would only mean that a larger number of mosquitoes took a single blood meal Here also the effect of wind will

mosquitoes, which are very
capable of flight against the
human blood meals

The chance of contact between man and mosquito will also vary considerably with differences in the liv ... If the people are poor and live in dark ill-
in the corners of the huts during
almost uninterruptedly on their hu
chances of transmission will be e
people are well-to-do and live in well-lighted and well-ventilated hous
ght, they will have
the house, have to
obably not return,
of the once-fed
mosquitoes and the chances of a second feed being taken are considerably reduced If in addition protective measures are used by the people, the chances are reduced still further, but this is a personal matter and will be considered below

Zoophilism or animal deviation is undoubtedly an important factor although there are different schools of thought on this subject. The original view expressed by Roubaud was that the proximity of cattle deflected mosquitoes from their human hosts, but the evidence on the subject has been confusing and it is obvious that in some circumstances cattle attract mosquitoes to their vicinity and thereby favour malaria transmission amongst the people living in close association with them. The fact that some species that are known as potential vectors and yet are

of enlargement is a good indication of the extent of the parasitic infection, whereas others claim that the reverse is usually the case The writer takes the view that splenic enlargement is evidence of imperfect host-parasite adjustment In hyper-endemic areas, immunity in the child is low, parasitic infections are heavy and considerable splenic enlargement is the rule In the well-nourished adult, immunity is high, parasitic infections though common are light, and the spleen is small Finally, in the ill-nourished adult of the poorer malarious districts, immunity is again low, and parasitic infection is kept down only by the continuous parasite—and incidentally red-cell—destruction by the hypertrophied reticulo-endothelial tissues, so that splenic enlargement and anæmia characterize the clinical picture

Macroscopically, in very acute cases, the spleen is *moderately* enlarged, dark red and congested, the capsule which is under pressure retracts when it is cut and a dark red substance oozes out In less acute cases, it is moderately enlarged, firm and slate coloured, when cut, the capsule does not contract in the same way, but a certain amount of black tarry sub- n the slate-coloured cut surface In chronic ilarged, the capsule is thickened and shows the organ may weigh anything up to 10 pounds, but it is firm, not very dark, and shows white fibrous trabeculæ

Microscopically there is a general hyperplasia in which both 'ements take part, later, there is an ssue at the expense of the malpighian cells are loaded with red-cell and parasite debris and hæmozoin pigment, but, in chronic malaria, parasites may be absent and pigment very scanty

Other organs —The liver is enlarged, the gall-bladder is distended, and on section the liver may show a dark red surface, but in certain cases in which there has been very excessive hæmolysis (*e g* blackwater fever) *there will be a distinct yellowish colour, the result of hæmosiderin staining,* in addition to the dark brown of the specific hæmozoin pigment The organ gives a marked prussian-blue reaction with potassium ferrocyanide Under the microscope the Kupffer's cells are seen loaded with pigment and debris and the bile canaliculi are dilated, in more chronic cases there are degenerative changes in the parenchyma cells

The active **bone marrow** is dark red, but the hyperplasia is mainly confined to the phagocytic reticulo-endothelial cells, which contain pigment and debris, to the detriment of the specialized hæmopoietic tissue *Parasites are usually present in fair numbers, but, from biopsy experience,* there is no reason to believe that there is any particular aggregation of parasites in this site

In fatal malignant tertian infections with cerebral symptoms, there

forming a granulomatous area around an arteriole usually in the cortex. The blocking of the arterioles is caused by a chemico physical change in *the blood elements*, an increase in stickiness of the parasitized red cells resulting from fibrin deposition which causes them to aggregate in large masses, and a local hæmo concentration due to plasma filtration into the tissues This blocking of the arterioles is seen best in a smear made by crushing a small piece of brain cortex between two slides and staining them by Giemsa's method

The kidneys are congested in acute cases but do not as a rule show any characteristic changes there are however cases of acute and sub-acute nephritis of undoubted malarial origin, and the rarity of this complication suggests that it may be an allergic phenomenon due to sensitization by the foreign proteins from parasite and tissue destruction in a previous attack. The kidney changes in the sub-acute attack are of the glomerulo-tubular nephrotic type. In blackwater fever (q v) there are characteristic changes.

There may be blocking of the arterioles in other organs and tissues of the body e g the pancreas and intestinal mucosa, these cause the protean localized manifestations of malaria such as malarial dysentery and a condition simulating acute pancreatitis.

The degenerative changes attributed to the malarial 'toxin' that occur in many organs are too indefinite to discuss in detail. It is very often doubtful if the changes noted are really due to the malaria or to some concomitant condition.

The blood.—There is nearly always some anæmia; the degree will depend on the duration of the attack and on other circumstances but it is disproportionate to the number of the red cells that have actually been destroyed by malaria parasites, and in the acute infection there is evidence of depression of hæmopoietic function of the bone-marrow. There is additional indirect evidence for this; the deduction is made from the fact that before treatment is given, though there is anæmia there is at first no rise in the percentage of reticulocytes, but that about six to eight days afte[r] specific treatment has been instituted there is a sharp rise in reticulocyte[s] (evidence of sudden active regeneration of red cells), suggesting that som[e] depressing influence has been lifted. These studies have been made most[ly] in Great Britain and in primary induced malaria; we have not been a[ble] to confirm them in malaria in an endemic area. On the other hand [we] have found that the bilirubinæmia is very frequently not as high as [one] would have expected had the anæmia been solely the result of red [cell] destruction, that is to say, had it been a hæmolytic anæmia.

The anæmia is usually normocytic.

There is a slight fall in leucocytes which starts just before the cl[inical] attack; the leucopenia is maintained throughout the attack and som[etimes] for some days after the temperature has returned to normal; the[re is] usually about 5,000 leucocytes per c.mm (see figure 11). The def[icit] is mainly in the granulocytes and there is usually an increase in large mononuclears. In the absence of kala azar and an actual as well as a relative increase in large mononuclear certain rarer blood diseases, a large mononuclear count of 15 per cent or over is said to be diagnostic of present or past malaria.



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fal
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The van den Bergh indirect reaction may be slightly increased during an acute attack, but it is not constantly so.

The blood sugar is reduced.

The erythrocyte sedimentation rate is much in creased whilst the infection persists.

(The specific findings, malaria parasites, pig ment and Schuffner's and Maurer's dots are discussed under the heading of diagnosis.)

The urine—During the febrile attack, the urine is usually concentrated and exhibits the ordinary 'febrile' characteristics

Urea excretion is increased and the chlorides and phosphates are often diminished

Urobilin is increased considerably during the attack There is quite frequently a trace of albumin at the onset, and in some cases of both quartan and malignant tertian malaria—traditionally in the former, but in the writer's experience just as frequently in the latter—a heavy cloud of albumin and granular and hyaline casts

Quinine albuminuria was not uncommon when large doses of quinine were the rule, but, with a maximum of 30 grains a day, this seldom occurs

Wasserma
undoubtedly g
Webb and Ki
and both tests in 23, of 25 induced malarias From his experience with naturally acquired malaria, the writer is convinced that this so-called 'false-positive' Wassermann reaction frequently occurs in this disease, it is usually transitory but may persist for some weeks It is however certainly not as constant a finding as the experience with induced malaria, quoted above, *would suggest*

SYMPTOMATOLOGY

Introduction—The clinical manifestations of malaria are so protean that it

Incubation period—The first symptoms do not appear until the malaria infection has reached a certain critical level, this is usually given as about 100 million parasites

The variations in the incubation period in different species are explained by simple arithmetic Let us take the cases of malignant tertian and quartan, and sup ... human host and was allowed to multi ... suppositions but they will serve our ... average rosette contains 24 merozoite ... lied by 24 every 48 hours and the 100 million mark will be passed in 12 days, whereas in quartan, with an average of 10 merozoites per rosette which matures every 72 hours, it would take 24 days to reach the critical figure of 100 million parasites Many merozoites of course fail to reach a red cell and are destroyed, and there are other factors which put a brake on reproduction, but it is easy to see why malignant tertian with its maximum production of 32 merozoites may have a very short incubation period and why quartan with its low merozoite production and 72-hour cycle is likely to have the longest

The incubation period of benign tertian is usually about 14 days, in malignant tertian it may be as short as eight days and is usually less than ... Recent work with malaria therapy

Prodromal symptoms before the actual onset are not uncommon, lassitude, anorexia, headache and a slight sense of chilliness, if the

temperature were taken, a low pyrexia, 99°F or so would probably be found In cases under close observation, a daily, or a 48 hourly, rise up to 99°F is the rule, these small rises in temperature correspond with the bursting of successive crops of rosettes before the infection has quite reached the true clinical threshold

The true onset is sudden, there are three stages in the attack —

The rigor —There is a feeling of extreme coldness, the patient shivers from head to foot sometimes shaking the whole bed, the teeth chatter, he pulls over himself all the blankets he can reach but it makes no difference to his feeling of coldness, the skin feels dry and the condition known as goose flesh is common, the features become pinched and he has the blue appearance of a cold person All this time the temperature is rising and after about an hour the shivering gradually ceases and the patient passes into the next stage

[illegible]

be prolonged

The sweating stage —The patient suddenly bursts into a profuse perspiration, the sweat pours from him A feeling of great relief comes over the patient and all the symptoms of the previous stage disappear The temperature falls and may be sub normal He now feels 'washed out' and tired and will usually go to sleep When he wakes up he feels perfectly well and is often prepared to get up and go about his ordinary daily routine

The whole attack occupies six to ten hours The rigor coincides with the bursting of the rosettes When a rosette bursts, there is a sudden release into the blood stream of not only the merozoites but of red-cell debris and probably certain products of malaria parasite metabolism The rigor is an anaphylactic phenomenon sensitivity having been worked up by the bursting of the earlier crops of rosettes Manson-Bahr states that the attack usually occurs in the morning, but this is not the experience of the writer, it may occur at any time

The periodicity of the malarial attack —This is dependent on the plasmodial cycle so that in tertian malaria it will occur every 48 hours and quartan every 72 h[illegible]



Figure 12 Benign tertian malaria

burst on the even days of the month and the other crop on the odd days, so that the patient will have a rigor daily (Hippocrates' quotidian malaria), or, if the infection is quartan, on two days out of three

In the initial attack of benign tertian malaria in a non immune the onset may be with a typical rigor, but much more frequently there is a daily

Benign tertian malaria shows a far greater tendency to relapse after treatment than malignant tertian Figure 15 shows the times when relapses usually occur In benign tertian malaria, the late relapse, the peak of which occurs at about the 28th week, probably accounts for the spring rise in malarial incidence that has been reported in some countries where the temperature precludes transmission at this time of year

Other specific clinical characteristics —It is by no means always possible to distinguish between the four different malaria infections clinically, except where quartan periodicity is clear, but the different infections have their special characteristics

In malignant tertian the temperature chart much less frequently follows the classical form It is usually remittent and not intermittent, and quite often the temperature is maintained at a high level for 36 hours only falling a few hours

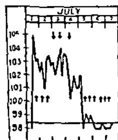


Figure 16 Malignant tertian malaria showing sustained rise despite treatment Oral administration failed to control fever, this necessitated three intravenous injections
↑ = oral quinine
↓ = intravenous quinine

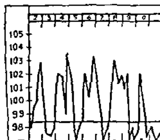


Figure 17 Malignant tertian malaria showing tertian periodicity

and, though spontaneous remissions obviously do occur (or the mortality would be much higher than it is), the danger of cerebral symptoms supervening precludes experiments in patients under observation to ascertain how soon remission will occur Relapses after adequate treatment are not common but when they do occur are likely to be as serious as the initial attack

Figure 18 shows that, if a relapse is going to occur, it will usually occur within the first few weeks

Quartan malaria is usually no more severe than benign tertian, splenic enlargement is less marked, but nephritis is said to be much more common, in some places it has been reported in 40 per cent of the cases, the albumin in the urine showing an increase with each attack.

Malaria due to *Plasmodium ovale* is very mild shows a marked tendency to early spontaneous remission, and responds rapidly to treatment

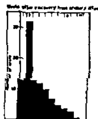


Figure 18 Time of relapse of 63 cases of malignant tertian

In an endemic area where more than one species of parasite occurs mixed infections are very common In Calcutta, where many cases of malaria are seen, it sometimes takes us many weeks to find what appears to be a pure benign tertian infection, even then, though many films have been searched and only benign tertian parasite found, this blood injected into another man, for purposes of malaria therapy,

will often give rise to a mixed infection, with the dangerous malignant tertian predominating

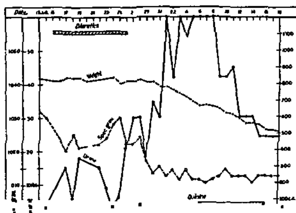
Other signs and symptoms of the ordinary attack —The *spleen* enlarges during an attack and subsides between attacks, but this frequent enlargement leads to hypertrophy and it tends to become larger at each successive attack The spleen may not be palpable during the first few febrile attacks of a primary infection, but in re-infections or relapses it provides a valuable indication of the nature of the fever The spleen has been known to rupture spontaneously during a malarial attack, there is a sudden severe pain in the abdomen, but this is quite often not in the splenic area (*see* also Diagnosis)

...k and congestion of the liver ... ery frequent symptom, this ... *confusion with amœbic* hepatitis

A feeling of pressure in the thighs and legs, and sometimes actual pain *in the legs are symptoms well recognized by patients subjected to frequent* malarial attacks

T ... pleocholia, followed by ... An icteric tinge of the ... al in severe malignant ... e if the patient is not ... aria by no means rare

Acute r ... *infection* ... this conditi ...



In infants the temperature will seldom run the usual course, it is nearly always a high remittent or even continuous fever, but shows great irregularity Vomiting occurs early and is frequent. The spleen enlarges rapidly and usually the liver also Convulsions replace the rigor that occurs in an adult Very prompt vigorous treatment is necessary, as early death due to hyperpyrexia and cerebral involvement is common, but a comatose child will often come round completely in a few hours

In pregnant women malaria if left untreated will be fatal to the child and dangerous to the woman Still-birth and abortion are very common, these are sometimes said to be due to the blocking of the placental vessels with subsequent separation of the placenta This is not the mechanism, since the parasites do not normally reach the placental circulation The

parasites seem to have a particular affinity for the decidual blood vessels, the placenta after parturition will case in which few were to be The decidual vessels are, however, too large to allow blocking by malaria parasites, and the abortion is more likely to be the result of some toxic effect Malarial subjects are more liable to the toxæmias and to the severe macrocytic anæmia of pregnancy It is imperative therefore that treatment should be undertaken immediately malaria is diagnosed in a pregnant woman

SPECIAL CLINICAL TYPES OF MALARIA

A *Pernicious* —This is usually associated with malignant tertian infection, but sometimes with quartan and even benign tertian The different forms that pernicious malaria may take are almost unlimited, but those most frequently encountered can be grouped as follows —

(i) *Cerebral forms* — (*a*) The heat centre may be affected, the

febrile symptoms

The other symptoms associated with the cerebral type are a full bounding and rapid pulse, a flushed face, sighing respirations, and vomiting

In these cases the differential diagnosis from heat stroke, apoplexy, epilepsy, diabetic coma, meningitis, alcoholism, and trauma may be difficult

(ii) *Algid forms* —There may be sudden collapse with no other symptoms or this collapse may be associated with hæmorrhagic vomiting, cramps and suppression of urine, mucus in the stools, or with other sting for example, hæmorrhagic

The characteristic symptoms in the algid form are collapse, a weak thready pulse, sometimes barely perceptible, a cold clammy skin, a weak voice, and slow shallow respirations The patient may recover fairly rapidly or may pass on into a 'typhoid state' for some days The localizing symptoms are due to the blocking of the arterioles by malaria parasites in the particular locality, as occurs in the brain in the cerebral forms

(iii) *Bilious remittent fever* —This is a form of severe malignant tertian malaria that was distinguished clinically from the ordinary malarial attack in the days before the parasite was discovered It seems less

fever, this will increase It is distinguished from its early appearance and conditions jaundice does n particular, it increases steadily

(iv) *Blackwater fever* —[This will be considered separately]

(v) Other types that do not fall into any of the above groups are the cardiac and the broncho-pneumonic They are self-explanatory

B **Chronic malaria** —This term is falling into disfavour with the malariologist, probably rightly so, because its exact meaning is not clearly defined There is, first, the chronic relapsing malaria that is usually simply malaria that has been inadequately treated *Even after a full course of cinchona, the relapse rate in benign tertian is high and the treatment* may have to be repeated for two, three, or even more relapses, but eventually it will respond It is surprising how many people there are, including doctors, who after a single infection will allow themselves to suffer for years for want of adequate treatment

In the next group are those persons who are subjected to repeated ... *are not necessarily*
... those that are infected
... seasonal, and those
that are infected perennially This subject has not been sufficiently studied and the different reactions of the individual to these repeated infections
... found in the
... to suffer very
... spleens, which
... *tion, and they*
...) There are
others who suffer periodic attacks of fever, are weak, debilitated, and anæmic, have enlarged spleens, are very subject to other infections, and are altogether of poor value to the community, on proper treatment, these patients will recover completely and again become really useful members of society

Finally, there is the **chronic malarial cachexia** The patient has a *huge spleen and liver, œdema and often ascites, he is very anæmic,* has an earthy complexion and often some jaundice, he may or may not have low fe...
of
en...
not being due to malaria but to other infections, such as kala azar or bilharziasis, but this sequel, as perhaps it should be called to malaria is undoubtedly *very common* in many endemic areas, though parasites are not often present and the patient does not respond well to anti malaria treatment

What determines the different reactions to malaria infection in ...

ryot on a very poor diet ...
the different stages of chronic malarial morbidity up to the stage of malarial cachexia

C **Latent malaria** —This is an interesting and sometimes important phenomenon of malaria infection It may be commoner than we imagine, but it can only be demonstrated properly in a person who leaves the place where he has been infected and lives in a malaria-free country It is not uncommon in people *returning home* from the tropics when they are subjected to the rigours of an *English winter; other* physical strains, such

to give a course of cinchona as a routine measure before the confinement of or a surgical operation on anyone coming from a highly malarious area

DIAGNOSIS

The diagnosis should be considered under five headings—the history the fever the spleen the blood film and response to therapy

A The history —Before making a diagnosis of malaria one should be satisfied that the patient at some time even if not recently has been in a malarious country Latent malaria will seldom if ever make its first appearance more than a year after infection the last possible chance that the patient had of being infected should be carefully ascertained

in the tropics without having a single attack of malaria

A history of a previous attack is also suggestive but here again it is necessary to be cautious because to the layman in the tropics fever is synonymous with malaria and the patient should be questioned as to whether a diagnosis was made on a blood examination whether the typical rigor and malarial periodicity were exhibited and whether there was response to cinchona (or mepacrine) Undue weight should not be given to the answer to the last question

B The fever —The classical fever charts of tertian and quartan

and is not usually maintained for any length of time

On the other hand malaria must not be excluded just because the temperature chart does not conform to any of the classical types and rigors are absent the chart may take almost any form in uncomplicated malaria and malaria may be complicating any other disease

C The spleen —There are many other diseases in the tropics that

portant to know if the
Rapid enlargement
ack and intermission
leen is slightly tender
pleen of typhoid In

chronic malaria as the spleen enlarges it becomes firmer and eventually assumes a wood like hardness as a result of the fibrotic changes that have taken place in these stages it is not tender

In tropical practice unless the spleen is palpable with the patient lying on his back with his legs drawn up or standing and bending forward slightly

the enlargement is not usually of much importance, the apparently painful contortions sometimes depicted in textbooks are not to be recommended

D The blood film —The examination of the blood film is the most important procedure in the diagnosis of malaria

Even one or two doses of cinchona or other anti-malarial drug will make the finding of parasites very difficult, so that the blood should be taken *(but not necessarily examined) before* any such drug is given

Whilst one would not recommend postponing the taking of the blood film, it should be remembered that immediately after a rigor, though the parasites will be most numerous, the large majority will be very young, and therefore very small, rings, these are not as easy to find as the larger trophozoites of some hours later (It is on this principle that the so-called

no actual multiplication takes place)

Methods of examining the peripheral blood —The blood can be examined by the thin film, the thick film, and the so-called cultural methods The last-named is a refinement
investigation is being carried c
'culture' cannot be accepted
parasites It is not a method
cedure, and it need not be described here

The Romanowsky-stained thin film is the method most frequently used, but the thick-film method is gaining popularity as the technique of
of the thick-film method is that a much
ined and a scanty infection, especially of
The disadvantages are that the number
so accurately, that the parasites them-
annot be
s their
species may rem ed cell
such as size, st ot seen
so readily For made

parasites *are found in the latter* and their identity is uncertain, a return to the thin film can be made and this re-examined with more confidence It is much easier to find parasites when you know they are there, than when you just think they may be there

the thick film for the

the *exact number of parasites*, this is easily and accurately done by ing with the blood an equal quantity of fowl s blood-corpuscle suspension of known concentration

A thin blood film is then made from the mixture, this is stained and field by field the number of fowl s red corpuscles (easily distinguished by their oval shape and nuclei) on the one hand and malaria parasites on the other are counted

The ratio of one to the other is worked out and as the number of fowl corpuscles per c mm is already known, the number of malaria parasites can be calculated

Finally, the giving of adrenaline to cause a contraction of the spleen, so that parasitized red cells in the spleen sinuses are forced into the circulation, is a method worth employing in hospital cases, when parasites cannot be found by any of the above methods Either 0 5 c cm of 1 in 1,000 adrenaline should be given subcutaneously, 20 minutes before, or 0 01 c cm intravenously, five minutes before the blood is taken, the latter will be more effective

Technique—The first essential in making a good thin film is to have perfectly clean slides and a good spreader The coverslip of a hæmocytometer makes an almost ideal spreader Otherwise one should select a good thick microscopic slide with a good edge and cut off the two corners* to make the spreading edge slightly narrower than the slide on which the film is to be spread

The blood can be taken from the lobe of the ear or the finger The part should be previously sterilized with alcohol and ether but it must be allowed to dry completely or be rubbed with dry sterile cotton wool The needle, which ... must be similarly ... the drop of blood ...ches the drop but

... the slide (figure 20)

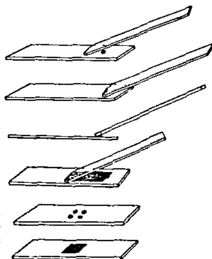


Figure 20 Methods of making thin and thick films

proof slide box for staining at a later date The unstained slides must never be left uncovered on the working table as blood is readily eaten by flies during the day and by cockroaches at night

Romanowsky stains especially those as modified by Leishman Wright Jenner and Giemsa are the most satisfactory All these stains depend for their action on the compounds formed by the interaction of methylene blue and eosin and the differences between the various stains are dependent on the proportion of the two dyes The fluid stains except Giemsa's stain are prepared by dissolving the dry powder in acetone free pure methyl alcohol so that a preliminary fixation with methyl alcohol is only required in the case of Giemsa's stain Leishman's and Wright's stains are used in the strength of 0 15 per cent and Jenner's stain in the strength of 0.5 per cent

* This can be done by making a scratch across each corner with a glass cutter or very simply by holding the slides under water in a basin and cutting off the corners with an ordinary pair of scissors

Preparing Leishman's or Wright's stain.—Stains in powder or tablet forms and extra-pure acetone-free methyl alcohol for dissolving them should be obtained from some reliable firm We have found the Gurr's* stains to be very satisfactory.

All the glassware used in preparing the stains and in storing them should be scrupulously clean and free from any trace of water, *they should be rinsed first* with absolute alcohol and finally with a little methyl alcohol

Staining with Leishman's or Wright's stain—Put the slides on a staining rack *taking care that the side with the blood film is upwards, also see that the two ends* of the slides are in the same plane

From a drop bottle, or with a pipette, pour on sufficient stain to cover the whole of the film, wait for one minute to allow for proper fixing, with a capillary pipette now add two to three parts of distilled water (pH 6.8 to 7.0) or the buffer solution† With another capillary pipette or glass rod thoroughly mix the stain with the diluent to ensure of uniform mixture over the film

When the mixture is allowed to settle, a scum will form on the top, if the proportion of the stain and diluent is correct Allow the diluted stain to act for 5 to 10 minutes

The diluted or undiluted stains on the slides must not be allowed to dry up at any stage of the staining Drying is prevented by covering the staining rack with a wide bell-jar, or other improvised device, this is a very necessary precaution in hot dry climates

When the staining is complete, wash off the excess stain with a generous amount of the buffer solution Tap water *may* be as satisfactory, but this varies from place to place so that its suitability must first be tested This will wash off all the stain

When it is dry the slide is ready to be examined

Staining with Giemsa's stain—It is more difficult to prepare this stain and it is better to purchase it in solution Giemsa's stain as prepared by Gurr is very satisfactory

For staining with Giemsa's stain, *preliminary fixing with methyl alcohol or some* other fixative is absolutely necessary

The optimum appearance of Giemsa-stained slides can only be learned by experience, but it is best described as a rich purple

Preparing dilute solution—Take about 20 c cm of prepared distilled water (pH 7.0) or buffer solution in a clean transparent glass cylinder, add 20 drops of undiluted stain or in other words as many drops of stain as there are cubic centimetres of water Mix well by inverting the cylinder and see that the depth of colour of the mixture is such that, *when held in front of the eyes, it allows* a distant object to be seen through it

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* *George T Gurr, 136 New Kings Road, London, S W.6, England*

† Monopotassium phosphate—6.63 gm
Anhydrous disodium hydrogen phosphate—2.56 gm (or 6.46 gm of $Na_2HPO_4 \cdot 12H_2O$)
Distilled water up to 1 litre
Add 1 c.cm of chloroform as preservative

he slide with methyl do s not dry up on minutes remove the

Now flood the slide with the d luted stain cover with a bell jar and allow the stain to act for at least half an hour or better still leave it overnight Next morning wash and dry the sl de as suggested above

Staining —Two methods of staining the thick film are described The former

Method I—The film should be allowed to dry for two hours at room temperature or in a bacteriological incubator (37 C) for one hour

Dehæmoglobinize the film with the following solution —

2.5 per cent solution glacial acetic acid	4 parts
2 0 per cent solution crystalline tartaric acid	1 part

This mixture keeps indefinitely it should be kept in a glass-stoppere l bottle

Lay the film on the stain ng rack and gently flood it with the mixture This process should be watched as thick patches will take longer than the rest to denæmoglobinize complete dehæmoglob nization is indicated by the whole film becoming greyish white

As soon as dehæmoglobinization is complete drain off the fluid by gently tilting the slide Flood the slide with methyl alcohol an l allow this to remain for five minutes The film is now dehæmoglobinized and fixed

Drain off the methyl alcohol and wash the film very thoroughly with neutral or very slightly alkaline distilled water Every trace of acid must be removed

Stain the film with d lute G emsa s stain one drop to each cubic centimetre of distilled water for 20 minutes or longer Wash in d stilled water Do not blot the film but let it dry by slanting it against a vertical surface film side inwards

Method II—For this method two solutions are required —

Solution A

Methylene blue	0.8 gm
Azure I	0.5
Disod um hydrogen phosphate (anhydrous)	5 „
Potassium dihydrogen phosphate (anhydrous)	6.25 „
D stilled water	500 c.cm

Solution B

Eos n	1 gm
Disodium hydrogen phosphate (anhydrous)	5
Potassium dihydrogen phosphate (anhydrous)	6.25
Distilled water	500 c cm

Preparation of solutions—The phosphate salts are first d ssolved then the stain is added Solution of the granular azure I is aided by grinding in a mortar with a small quantity of the phosphate solvent The solutions of the stain should be set aside for two hours when after filtration they are ready for use Should a scum later appear on the surface or the dye precipitate on the stained films subsequent filtration is necessary

The sta ns are kept in covere l jars of such a size that the depth of the solution is about 3 inches, the level being maintained by the add tion of fresh stain as necessary Eosin sol ition should be discarded if it becomes greenish

Technique (i) Dip the film for about three seconds* [illegible]
(ii) [illegible]
(iii) [illegible]
(iv) [illegible]
(v) Place *vertically* against a rack to drain and dry

N.B.—The American equivalent of the German azure I is azure B†

Identification of the parasites.—(*See* plate B, frontispiece) In the thin film, the parasites, especially the larger forms, will be found mostly at the tail end of the film They are always within the red corpuscles, though the larger forms occupy practically the whole of the corpuscle and only a shadow-like ring or segment of a disc represents the remains of the host cell

The **ring** is the form of which the largest number appear in the peripheral blood, the young ring form consists of a ring of light-blue cytoplasm with a vacuole in the centre and a dark-red chromatin dot at one point on the periphery The chromatin may take a rod like form or appear as a double dot, and, though it is actually red, in a slightly over-stained film it appears almost black The ring forms of the different species differ, the smallest and most delicate is that of *P falciparum* and the forms of the asexual cycle seen in the peripheral blood in malignant tertian infection are usually young rings, but larger trophozoites will also be found in heavy infections, whereas the *P vivax* trophozoite is seen in all its stages in the peripheral blood and from the beginning develops an irregular amœboid appearance with a large chromatin mass As the parasite grows, the cytoplasm becomes more amœboid, sprawling all through the corpuscle and eventually almost filling it, pigment appears, the chromatin divides into irregular masses, and the unoccupied portion of the red cell shows fine eosinophil stippling known as Schuffner's dots *P malariæ* is not so amœboid but the ring is coarser than that of *P falciparum* and the chromatin globular rather than rod-shaped, the growing trophozoite usually takes the form of a band, with the chromatin in one mass and the pigment scattered, stretching across the red corpuscle which does not ordinarily show any stippling

The so-called *accole* form of *P falciparum* appears as a thin strip of cytoplasm attached to the surface of the cell

When the **trophozoite** is fully developed schizogony commences, the chromatin divides, and the parasite becomes a **schizont,** in *P vivax* the outline is now regular, the parasite is usually oval in shape and occupies about two-thirds to three-quarters of the corpuscle, the chromatin and pigment are scattered throughout the cytoplasm of the parasite, in *P malariæ, the schizont almost fills the corpuscle,* and the pigment granules are collected into a single mass

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[illegible]

(v) Filter before use

P falciparum unless there are at least 32 merozoites)

…he peripheral blood The … The most characteristic … *lciparum*) The crescent is much longer than the diameter of a red corpuscle, so that it appears to extend beyond the red corpuscle, the pale outline of which is to be seen in the concavity of the crescent The female is a long slender crescent, stains a dark blue, and has a compact nucleus around which the pigment is aggregated The male gametocyte is stouter and less characteristically crescentic, with a large nucleus the pigment scattered, and the cytoplasm staining a pale blue

The gametocytes of *P vivax* are not so frequently encountered in the peripheral blood, they are round or ovoid and fill the corpuscle, the chromatin is aggregated into one mass, the pigment is scattered, and if there are any visible remains of the red corpuscle Schüffner's dots will be seen The gametocyte of *P malariæ* is usually much smaller than that of *P vivax*, but otherwise very similar As in the case of *P falciparum*, the nucleus in the female is more compact, and the staining of the cytoplasm darker

The changes in the containing red corpuscles that occur are characteristic In benign tertian infection (*P vivax*), the cell is pale and considerably enlarged, and it exhibits regular fine eosinophil stippling throughout The red corpuscle that contains the very young ring forms of *P falciparum* is not enlarged and in fact may appear to be smaller than normal, but is really more globular When the trophozoite enlarges, however, the cell also enlarges slightly, becomes slightly darker, and shows numerous Maurer's dots, or clefts, these are red or purplish, coarser, and much more irregular than Schuffner's dots The red corpuscle in quartan (*P malariæ*) infection is similarly more globular but does not show Maurer's dots

The pigment in benign tertian is a fine and lightish brown, in malignant tertian it is coarser, black, and forms clumps, and in quartan, it appears early, is very prominent, and falls between the other two in the matter of colour and coarseness

P ovale has not been included in this description up to the present, as it is a comparatively rare plasmodium It is very similar to *P vivax*, except that it is not amœboid and the rosette contains 8 to 12 large merozoites, the red corpuscle which is only slightly enlarged shows more marked stippling than in *P vivax*, but is of a slightly paler red The special characteristic of the red cell in this case is the frequency with which it assumes an ovoid shape—it is from this and not from the shape of the parasite that its name is derived—or shows a fimbriated edge (This fimbriation must occur during spreading and is an indication of some characteristic physical change within the cell rather than of any changes in shape that occur *in vivo*)

Table I

Identification of species of malaria parasites

Parasite	*Changes in red cells*	*Pigment*	*Trophozoites*	*Adult schizonts*	*Merozoites*	*Gametocytes*
Benign Tertian (*Plasmodium vivax*) 48-hour cycle	Large and pale with fine red stippling (Schuffner's dots)	Fine yellowish-brown granules or rods	Rings ⅓ ½ diameter of red cell growing forms very irregular with pale blue staining and indistinct outline Vacuole present	Completely fills red cell Irregular in shape	Medium size, 14–24 in number	l or ovoid larger than ll ı deep blue staining asm and small compact s plasm stains more blue or reddish with paler nucleus
Quartan (*Plasmodium malariæ*) 72 hour cycle	Not enlarged No stippling	Coarse dark brown or almost black Appears early	Rings ⅓–½ diameter of red cell growing forms often band like or angular Cytoplasm dense early pigment	Fills red cell Daisy head rosette	Large size, 8 10 in number	l or ovoid the size ed cell is deep blue with small ompact nucleus s pale blue or pink ı large pale nucleus
Malignant Tertian (*Plasmodium falciparum*) 48 hour cycle	Not enlarged spherical and show coarse stippling (Maurer's dots)	Blacker than in other forms clumps early	Young forms are fine hair-like rings about ⅙ diameter of red cell with *2 chromatin* dots and *accolé* forms common Larger rings are also seen Growing forms very rarely seen	Extremely rare in peripheral blood as they *tend to adhere* to blood vessel wall	Very small Number variable 8–32 *or more*	entic staining deep vith a compact central s with pigment ıted round *it* ıge-shaped staining lue with larger and ıucleus and scattered ıt
Plasmodium ovale 48 hour cycle	*Very slightly* enlarged paler than normal Stippling like *P vivax* but coarser Ovoid or distorted fimbriated cells	Coarser than in *P vivax* Dark yellowish brown	Rings about ⅓ diameter of red cell not amœboid cytoplasm dense well defined chromatin large may be irregular	Mature forms slightly smaller than red cell daisy head rosette	Large size 8–12 in number chromatin sometimes *crescentic*	› *malariæ* in d red cells

To summarize, identification of the species depends on (i) changes in the red corpuscles, (ii) the nature of the pigment, (iii) the character of the trophozoites, (iv) the presence of the mature schizont—for they do not appear in the peripheral blood in malignant tertian (*P falciparum*) infection—and their character, particularly with reference to the number of merozoites in the rosette, and (v) the character of the gametocytes The data are summarized in table I which is a modification of the table given by Covell (1939)

Significance of the findings —The finding of a malaria parasite naturally indicates that the patient has a malaria infection, but it does not necessarily mean that all his symptoms are due to malaria, for he may have some other disease and malaria may only be an intercurrent infection, or his immunity may be such that the malaria parasites are not actually giving rise to any symptoms at all Again, the presence of one species of parasite, even if one is absolutely certain about its identity, does not preclude the presence ... writer had the experience of ... not only typical quartan ... and yet the recipient deve...

Nevertheless, the presence of parasites cannot be ignored from the point of view of treatment, even if one is certain that they are not the cause of the whole symptom complex

Conversely there are many occasions on which one will fail to find parasites in a true case of untreated malaria, as any honest protozoologist will admit The importance of making a definite protozoological diagnosis cannot be over-emphasized nor can one condemn too strongly the practitioner who assumes that all fever in a malarious country, or even in a malarial subject, is malaria Nevertheless, after a very thorough though unsuccessful attempt to make a parasitological diagnosis, it is sheer folly to withhold treatment in a case in which other evidence points to malaria

In the ordinary malarial attack parasites are usually present in the peripheral blood and are easy to find They may however be scanty and it is easy to overlook the fine rings of the malignant tertian parasite in a thin film, a thick film will help in these circumstances There are local variations to this rule, and in some localities the parasites in an ordinary case are very scanty in the peripheral blood Other circumstances in which the parasites are often difficult to find are, (i) at the beginning of a primary attack, (ii) in residents in an endemic area who have acquired a degree of immunity to local strains, (iii) in chronic malaria with splenomegaly and (iv) after a few doses of an anti malarial drug

Regarding the ide... worker often finds it parasite, but after ex... possible to find enoug... are however very common and may cause confusion

both directions, they may dismiss true pigment as an artefact for it looks very like foreign matter superimposed on a cell, or they may mistake stain debris and dust for hæmozoin pigment

The increase in large mononuclears to 15 per cent will be a point of diagnostic value in some countries, but will not differentiate malaria from certain other protozoal diseases, e g kala-azar, and in any case may only indicate past malaria

Sternal puncture —When the parasites cannot be found in the peripheral blood, it will often be worth using this method In some observers' experience it has been proved a valuable supplementary diagnostic method

isease in which

the As has been

said find parasites

in a case of malaria, when therefore there is any suspicion in the mind of the physician that the fever fro

he should prescribe a course of

the occasions on which this t

possible alternative diagnosis a

criminately in every case of fever occurring in a malarious country

If the therapeutic test is decided upon, an adequate course must be prescribed and unless a definite diagnosis of some other disease is made

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ite

course

There are few cases of malaria in which the fever will not respond to

conditions Therefore thou the

fever does not respond may very

dangerous to make a positive diagnosis of malaria on the therapeutic test.

DIFFERENTIAL DIAGNOSIS

The conditions which malaria may simulate are so numerous that a

be written to deal adequately with the

diseases from which malaria has to be

justifiable amount of space, therefore

ch the differential diagnosis of malaria

has to be considered with the most important examples in each case, are given —

Fevers *Short*—Influenza bronchitis dengue sandfly fever relapsing fever

ystitis malignant endocarditis kala azar

fevers Hodgkin s disease glandular fever

chronic inflammations

Splenic enlargements —Leukæmia splenic anæmia and syphilis as well as the febrile diseases mentioned above kala-azar typhoid etc

Anæmia —Ancylostomiasis hæmolytic and other anæmias

Cerebral —Heat stroke meningitis apoplexy epilepsy diabetic coma insulin shock alcoholism narcotic poisoning and trauma

Abdominal —Dysentery cholera appendicitis cholecystitis and liver abscess

Jaundice —Weil s disease yellow fever infective hepatitis and catarrhal jaundice

Cardiac pulmonary and nephritic conditions

TREATMENT

Historical—Cinchona bark which has been one of the indigenous medicines of South America probably for millenia, was first introduced into Europe as treatment for malaria according to tradition* by the Countess of Chinchon the wife of the Spanish Viceroy of Peru, about the year 1638 The fame of this bark spread rapidly—for those days—through the world and it was apparently introduced into India about twenty years later

The subsequent history of the drug in India is interesting for early in the nineteenth century it was almost entirely abandoned in the treatment of malaria This surprising occurrence is easier to understand if one remembers that the diagnosis of malaria was clinical only and that there are many other fevers that simulate it A long run of failures to get any response to cinchona therapy because the disease was not malaria might conceivably prejudice a physician against the drug Also as powdered bark only was used and not the extracted ... ported from ... herefore in ... the use of ... eve that a large number did not continue to use this invaluable drug surreptitiously The treatment that was advocated in its place was heroic purging with calomel in particular and of course blood letting Doses up to 60 grains of calomel were given and it was quite common for a patient to lose all his teeth from the mercurial gingivitis caused by this treatment

... the first half of t ... by the work that ... y the French cher ... brought from South America in 1860 and cinchona cultivation was started in India

In 1866 the Madras Cinchona Commission was formed to investigate the relative value of the various alkaloids of cinchona bark they came to the conclusion that quinine was the most useful alkaloid although the other crystalline alkaloids were also active in the treatment of malaria This important and scientifically sound observation had very serious repercussions later

The cultivation of cinchona flourished for some years in India and Ceylon until in the year 1887 Ceylon alone produced 16 million pounds of cinchona bark This uncontrolled growth of the cinchona industry led inevitably to the disastrous slump which ended in the ruin of the cinchona plantations so that by the end of the century cinchona planting as a private enterprise had ceased in India Java survived this slump and has enjoyed a virtual world monopoly in the cinchona industry ever since

In 1931 a committee of the League of Nations Health Organization laid down a minimum standard for a cinchona-alkaloids mixture that was efficient and at the same time could be prepared from the hardier cinchona plants without the prior separation of the various alkaloids or the addition of quinine this they called totaquina

After the war of 1914-18 the German chemists stimulated by the fact that they had no colonies in which they could grow cinchona attempted to find a synthetic substitute for quinine and in 1926 Professor Schulemann produced the quinoline compound plasmochin which important though it is has only a limited application in malaria therapy This was followed a few years later by an acridine compound which was given the name atebrin The writer had the *privilege of being the first phys* ... give a clinical trial to this drug a ... Medicine published the two first ... journal (Napier and Das Gupta ...

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*The Countess of Chinchon tradition has now been exploded (Haggis 1941) The Countess about whom the picturesque story is told never went to Peru and her successor who did never had malaria never used the miraculous bark, and never returned to Europe The true story appears to be that cinchona bark first reached ... bark which was ... locally The ... still retained

Cinchona requirements.—The world quinine requirements have been placed at 1,387,412 kilogrammes annually (League of Nations, 1932) In India, it has been conservatively estimated that to treat her one hundred million sufferers from malaria at least a million pounds of cinchona alkaloids are required About 70,000 lbs of cinchona alkaloids, of which

Cultivation in the Philippines has been developing during the last ... years There is now little cultivation in South America, the natural home of cinchona No other country produces cinchona in any significant amounts

The cinchona alkaloids.—Cinchona bark contains four crystalline and a number of amorphous alkaloids The four former, quinine, cinchonine, quinidine and cinchonidine, all have anti-malarial properties Of the individual alkaloids, quinine is undoubtedly the most valuable, as it is the most powerful and produces the least adverse by-effects Of the other

...he most use-
...nchonine if
...tract, and
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...samples of
...per cent, as
...per cent of
...s alkaloids

have a poor anti-malarial action and tend to make the tablets—a convenient form in which the mixed cinchona alkaloids are often given—hard and insoluble

Quinine salts.—Quinine base being very insoluble, the drug is usually given in the form of one of its salts The most generally useful is the sulphate, though it is not very soluble in water and has to be prescribed with acid in the mixture The bihydrochloride is the most soluble, but, making a very acid solution, it causes pain when given intramuscularly, and therefore the neutral hydrochloride salt is preferable for this purpose

The dihydrobromide is conveniently soluble, but contains a smaller amount of the alkaloid and therefore 25 per cent should be added to the dose when this is prescribed in the place of the sulphate, and more when it replaces the bihydrochloride It is reported to give rise to less cinchonism, but possibly this is accounted for by its lower alkaloidal content

The ethyl carbonate is insoluble in saliva and therefore tasteless, but it dissolves in the normal gastric juice It is not however fully absorbed and it is generally stated that 8 grains of the ethyl carbonate of quinine (euquinine) correspond to 5 grains of the sulphate

The strength, solubility, and reaction of the commoner salts of quinine are as follows :—

Salts	Percentage of quinine base	Solubility in H_2O at 25°C	Reaction
Sulphate	74	1 in 720	Neutral
Hydrochloride	82	1 in 18	"
Bisulphate	59	1 in 8	Strongly acid
Bihydrochloride	82	1 in 0 75	" "
Dihydrobromide	60	1 in 6	Neutral
Ethyl carbonate	82	nil	Alkaline

species of cinchona, these vary
ona ledgeriana gives the highest

There are other plants, e.g. the hybrids *C. officinalis* and *C. robusta*, that whilst they have a comparatively high alkaloid yield though short of that of *C. ledgeriana*, are very much hardier than *C. ledgeriana*, and will grow over a much wider range of climatic conditions.

Totaquina standard.—The standard laid down for totaquina (introduced into the *B.P.* 1933) is that it shall contain at least 70 per cent of crystalline alkaloids, of which 15 per cent must be quinine, the amorphous alkaloids must be less than 20 per cent, mineral matter less than 5 per cent, and moisture less than 5 per cent. The cinchona febrifuge grown in the government plantations and prepared in the government factories in Bengal complies, for all practical purposes, with this standard. A recent analysis of a sample showed that it contained 32 per cent quinine, cinchonine 11 per cent, quinidine 1 per cent, cinchonidine 30 per cent, and amorphous alkaloids 15 per cent.

Cinchona policy.—One of the main reasons that Java gained and has kept this world monopoly was that they have large areas of country that are particularly suited to the growth of the high-quinine yielding varieties of cinchona plant, e.g. *Cinchona ledgeriana* and the world demand has during the last 50 years been almost entirely for quinine and not for the other alkaloids that might also be used in the treatment of malaria. It is natural that, if only one of the four available alkaloids is used and the others are more or less wasted, the price of the one alkaloid will have to be greater than if all four were saleable, for the planter must make his living. This has led to the price of quinine being comparatively high, and the high price of quinine is an important adverse factor in malaria control in rural areas.

A committee of the League of Nations Health Organization studied this question of the high price of quinine. They decided that although no country could hope to produce quinine in competition with Java, many could grow other cinchona plants that would produce a comparatively high yield of total alkaloids from which a preparation of mixed alkaloids of cinchona could be produced at a very much lower price than that of quinine. Another advantage would be that by growing these other cinchona plants on a large scale many poor countries could provide their own cinchona requirements and become independent of imported quinine. The committee realized that one of the reasons for the
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The unfortunate impression has arisen that cinchona febrifuge is a cheap and inferior substitute for quinine which is foisted on poor people who cannot afford quinine. *This was of course true of some but not of all cinchona febrifuges, and* the international totaquina standard has given us a means of distinguishing between the good and the bad preparations. Only such preparations that are stated to be of 'totaquina standard' should be used.

The next step taken by this committee was the organization of experiments to show the relative efficacy of totaquina as compared with quinine. These experiments have shown that totaquina is very nearly if not quite as efficacious as quinine in the treatment of malaria. The writer's experience has been that it is perhaps even more efficacious in benign tertian infections.

India was only one of the countries which the committee of the League of Nations Health Organizations had in mind, but in no country could their work have more important repercussions if the government would take advantage of

the situation Though India is not so fortunate as Java in her *climate, vis-à-vi*
the cultivation ... has neverthele
vast areas in w ... ould grow, and
the government ... to protect large
scale cinchona ... arter the presen
price of quinir ... become entirel
independent of imported quinine*

The synthetic anti-malarials —There is a very great future in this lin of chemical research *The initial successes that have been achieved ar* very encouraging, and we believe that when chemists and pharmacologist can again turn their full attention to this subject more efficient and les toxic compounds will be found

The first of the successful anti-malarial drugs to be synthesized wa plasmochin (*B P* pamaquinum), this is N-diethyl-amino-isopentyl-8 amino-6-methoxy-quinoline Originally introduced for the treatment of the malarial attack and the destruction of the asexual forms, plasmochin has now been found to be too toxic, in the doses in which it has to be given, for this purpose It is however the only drug that has any appreciable *direct action on the gametocytes, particularly those of malignant tertian.* Also it enhances the action of quinine and mepacrine in completely eradicating a benign tertian infection and thereby preventing a relapse In these two capacities, it acts in very small doses, far below the toxic level

Cilional, di-alkylamino-alkylamino-oxy-quinoline, a drug closely allied to plasmochin but *much less toxic, has an action similar to that of* plasmochin, it has however to be given in much larger doses to produce the same effect

Another successful preparation is atebrin (B P mepacrinæ hydrochloridum), or dihydrochloride of 2-methoxy-6-chloro-9-α-diethylamino-δ alkylamino-acridine This drug is *less toxic, in normally non-toxic doses*
it destroys the asexu ... and controls
the malarial attack, ... m
and has little and c ... e,
it is therefore similar in action to quinine

There are now a number of preparations that are apparently identical with atebrin, *e g* crinodora, quinacrine, and recently British and American firms have also placed on the market preparations that are chemically identical with plasmochin, *e g* præquine

Mechanism of actio ... dge on this
subject is not really ve
alkaloids act indirectly b

reduce their numbers or
schizonts, as these are

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* The writer as Editor of the *Indian Medical Gazette,* has for the last eleven years repeatedly urged the government to adopt a policy of extended cinchona growing and alkaloid distribution Early in 1942 the Japanese invaded Java and India's external source of cinchona *vanished It has been possible to increase* India's internal production to about 80 000 lbs a year which is about 8 per cent of the real requirements and 40 per cent of her average annual consumption for some years Recriminations are useless but the writer feels that he may be allowed just this one 'I told you so' The writer is informed that Mysore, Travancore and Ceylon are already starting cinchona plantations *and cultivation in the Government of India* plantations in Sikkim Bengal and Madras is *now* being extended

shortly after quinine administration It is suggested that the action may be on the merozoites whilst they are free in the blood, either directly or by altering the charge on the red cells so that the merozoites are not attracted to, or are unable to enter, the red cells The clinical evidence that the action of quinine is greater during the sporulating stage is inconclusive, the action on the sexual forms of *P vivax* and *P malariæ* is poor and on those of *P falciparum* is nil

On the other hand the action of atebrin is a direct one the molecule is attached firmly to the parasite which shows obvious signs of degeneration very shortly after the drug is given

Absorption and excretion—By whatever route *quinine* is given its eventual fate is much the same Given by mouth to a normal individual it is absorbed very rapidly and appears in the blood within 15 minutes and in the urine within about half an hour it reaches peak concentration in the urine in 5 to 9 hours and is practically all excreted within 24 hours

Atebrin also is absorbed very rapidly, but most of it is fixed in the tissues it is stored mainly in the liver spleen and lungs About one quarter of the total blood atebrin is in the plasma

A plasma level of 50 to 80 microgrammes is considered desirable for effective treatment this is usually reached within a few hours and is maintained if the newer intensive course of atebrin (*see* p 105) is given but plasma concentrations show wide individual variations

By whichever route it is given atebrin appears in the urine very early though not more than 3 to 4 per cent of the dose taken is excreted by this route excretion continues intermittently for many weeks after the patient has ceased to take atebrin About twice this amount is excreted in the fæces

PRINCIPLES AND AIMS OF SPECIFIC TREATMENT

It will be advisable first to analyse our aims in the treatment of malaria, and we must consider treatment in the widest sense that is, treatment to prevent as well as cure the disease The objects that we may hope to achieve by specific drug treatment can be placed under five headings —

(1) *True causal prophylaxis*, the destruction of the sporozoites injected by the mosquito before they enter the red cell and commence their intra-corporeal cycle

(2) *Clinical prophylaxis*, the administration of a drug that will prevent the infected person from suffering from an attack of clinical malaria, but without necessarily destroying all the parasites in that patient*

(3) *The treatment of the clinical attack*

(4) *Treatment to prevent relapses*

(5) *Gametocyte destruction in the cause of general prophylaxis*

(1) True causal prophylaxis that is to say the destruction of the sporozoites injected by the mosquito before they enter the red cell and commence their intra corporeal cycle

There is at present no drug which will achieve this Ten grains of quinine given daily for five days before and nine days after a person has been infected by a mosquito will not prevent the development of the parasite, nor will atebrin in full therapeutic doses followed by a daily dose of 0 1 gramme

In an experiment carried out in London, in which some half-dozen well-known malaria workers took part, three daily doses of 0 02 gramme of

*For this the army favours the expression 'suppressive treatment' There are points in favour of this term provided that it is not used in a disparaging sense as it often is The writer prefers the better established 'clinical prophylaxis

plasmochin (a dose which will sometimes produce toxic symptoms) were given for one day before and six days after the infective mosquito bite, and yet *five out of six of these men became infected*

The discovery of a drug that will act on the sporozoites would mark a great advance in malaria therapy

(2) Clinical prophylaxis, that is to say, the administration of a drug that will prevent the infected person from suffering from an attack of clinical malaria, but without necessarily destroying all parasites in that patient

Now this *can* be done A dose *of 0.2 gramme* (three grains of atebrin given twice a week, or a daily dose of six grains (five grains are sometimes insufficient) of quinine will usually keep a person free from clinical malaria, even in a very malarious place, for an almost indefinite period

[illegible]

in the table below In another group six grains of quinine were given da[illegible] to adults, and children were given smaller amounts, as shown in the table

Ages, years	Atebrin grammes	Quinine
1 to 2	0.025	or 0.1 g euquinine* (1½ grains)
3 to 4	0.05	or 0.2 g euquinine (3 grains)
5 to 6	0.075	or 0.2 g quinine bihydrochloride
7 to 8	0.1	
9 to 10	0.125	
11 to 12	0.15	
13 to 16	0.175	or 0.4 g quinine bihydrochloride

A third control group received no specific treatment The results of this prophylactic treatment are shown in figures 21*a* and 21*b* (Field, Niven and Hodgkin, 1937)

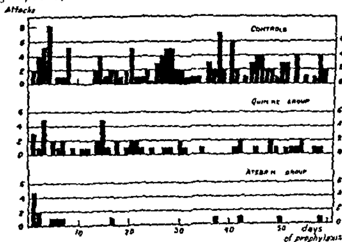


Figure 21*a* Immediate effect of prophylactic measures

It will be seen that in the atebrin series the malaria was controlled almost immediately and only an occasional case occurred in the quinine

* *Euquinine or quinine ethyl carbonate* is insoluble in the mouth and therefore tasteless, whilst it contains 82 *per* cent of the alkaloid actually more than quinine sulphate (74 per cent) its lower solubility in the gastro-intestinal tract makes it advisable *to give it in the relatively* larger doses indicated

series the control of the malaria was slower but eventually it was largely effected

The important point however is that even in the atebrin group, they

suffered a clinical attack of malaria almost immediately and nearly 80 per cent within two months

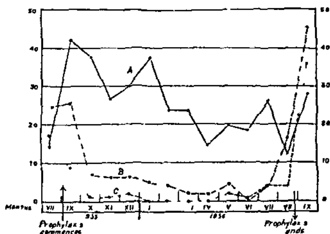


Figure 21b Monthly incidence of malarial attacks

		Number of subjects
A =	Controls	91 ± 14
B =	Quinine 04 gramme daily	91 ± 17
C =	Atebrin 04 gramme weekly	103 ± 12

This is shown in figure 21 which gives the malaria incidence month by month for more than a year It will be seen that when in the control group there were nearly forty cases monthly, in the atebrin group there were none or only one or two However, directly the prophylactic treatment was withdrawn the incidence in the atebrin group rose to 37 and was actually higher than in the control group Lamprell (1940) in a similar experiment in Assam obtained an exactly comparable result

ugs,
full
do
fec-
in

whom the infections were allowed to run their natural course and immunity was allowed to develop

It is thus apparent that drug prophylaxis in a labour force should only be carried out in special circumstances either as a stop gap whilst other anti malarial methods are being organized or as a temporary measure to keep the largest possible number of workers in the field during a particularly busy time of year, this second reason will apply to armies operating in

malarious countries, and the adoption of this measure might well determine the success of a campaign

[illegible]

other foreigner, is touring in a malarious tropical country, in such circumstances that he (or she) is likely to be bitten by a malaria-carrying mosquito, he should certainly take a prophylactic drug, and atebrin is in *this case probably the drug of choice, it should be taken* in prophylactic doses (p 98) during the whole stay in the malarious country and for a week after leaving it, after which a full therapeutic course should be taken (p 101)

(It should however be mentioned that though drug prophylaxis is most useful in the case of the casual visitor, it will actually be less effective in a non-immune individual than in one who has acquired some immunity through previous experience of malaria)

If this same person is residing for perhaps some years in a slightly malarious country he should not depend on drug prophylaxis, but take all other prophylactic measures (*vide infra*) to avoid infection, at the same time, if he is still running some risk of infection, drug prophylaxis should be used as an extra precaution, but in these circumstances, in view of our *lack of knowledge of the effects of atebrin over a very long period, the* writer would advocate quinine (six grains daily) again throughout the whole period of risk and for a short time afterwards

As the daily dose of quinine is not without its unpleasant and possibly mildly detrimental effects, it cannot be advocated lightly and in circum- [illegible] on,
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[illegible] *ile*
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[illegible] as
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in tropical countries are [illegible]

There is no reason to suppose that prophylactic quinine is ever seriously detrimental, or that it increases the risk of blackwater fever occurring in a subject who takes it, as has been suggested, it is not the regular taking of quinine that is the predisposing factor in this serious sequel of malaria, but the frequent omissions to take it

[illegible] permanent settler in a malarious
[illegible] axis should ever be at-
[illegible] periodical attacks, which
[illegible] *to allow them to work*
[illegible] lable to the general im-
[illegible] preventive measures

(3) ***Treatment of the clinical attack***—In the very great majority of cases, the clinical attack can be terminated easily and rapidly by the administration of atebrin*, quinine, or standardized cinchona febrifuge (*B.P* totaquina standard) given by mouth Plasmochin* has no place in treatment under this heading

* The writer has used the words 'atebrin' and 'plasmochin' in preference to the official 'mepacrine' and 'pamaquine', as the former are at present more familiar but the references are not necessarily to the proprietary preparations with *these names*

Before discussing specific treatment, mention must be made of a recommendation of the Health Committee of the League of Nations, which has been severely criticized, but with which the writer is in part agreement They recommend that in the *initial* attack of malaria the patient should be allowed to remain untreated for a few paroxysms in order that he may work up his natural immunity before he is given any anti malarial drug

This suggestion is based on reliable experimental evidence and it is no doubt absolutely sound advice, in theory, but in practice it is seldom possible to do this, as in most cases the patient's only desire is to be cured of the immediate attack, and if one insisted he would simply call in another doctor It is, in any case, only advocated in benign tertian infection

If cinchona or quinine are given the prescriptions should be —

℞ Totaquinæ (or cinchona febrifuge)	g x	or ℞ Quininæ sulphatis	g x
Acidi sulphurici dil	min xx	Acidi citratis	g xx
Magnesii sulphatis	g xxx	Aquam chloroformi ad	℥i
Aquam chloroformi ad	℥i		

One or other of these should be given twice daily in benign tertian infection and three times daily in malignant tertian infections and this dosage should be continued for seven days

If atebrin is used 0 1 gramme (or 1½ grains) should be given three times a day for five days—or in severe malignant tertian infections this may be continued for seven days, but not longer

For women and small or weak men, this dosage may be too high, and it may be advisable to reduce the 10 grains of quinine to 7½ grains, in each case the adult dose of atebrin is usually well tolerated

Children both need and are able to take relatively larger doses of quinine than adults, the dose in grains is calculated as 1 to 1½ *plus* half the age of the child in years (*e g* give a well-nourished child of five years of age 1½ + 5/2 = 4 grains) This is best given, twice or thrice daily according to the species of the infecting plasmodium, in treacle or honey, preferably in the form of the tasteless (euquinine), but if this salt is given the dosage must be increased by 50 per cent

The *total* daily dosage of atebrin for children should be

1 to 2 years	0 05 gramme	(¾ grain)	9 to 12 years	0.2 gramme	(3 grains)
3 to 4 „	0 075	(1¼)	13 to 16	0.25 „	(4)
5 to 8	0 1	(1½ „)	Over 16	0.30	(4½)

The total dose is divided into two or three individual doses as is most convenient

In the very great majority of instances oral administrations will be sufficient and effective The reason for this is that when the drug is

is no response to oral administration and the various reasons for this are given below

(ii) Faulty preparation of the tablets, that is, they may be insoluble through the presence of too much amorphous alkaloids, or because they are coated with some insoluble substance

(iii) Vomiting of the mixture or tablet

(iv) Failure of absorption by the gastric mucosa

(v) Deception by the patient himself, or herself, on account of prejudice (pregnant woman) or malingering

The methods that can be recommended to circumvent some of these occurrences are to test the stock mixtures by means of the *simple method* originally suggested by Megaw, and to test the urine of the patient by the Tanret-Mayer test for the presence of quinine, or for atebrin by the method of Tropp and Weise (1933)

Test for quinine in mixtures—The reagent is made up as follows —Pure phosphotungstic acid—1 ounce dilute sulphuric acid—5 ounces and rectified spirit—12 ounces Place 2.5 c cm of the reagent into each of two narrow tubes add to one 0.25 c cm of the quinine solution to be tested and to the other 0.25 c cm of a control mixture containing the amount of quinine that the mixture was supposed to contain *e g* 10 grains to the ounce A *precipitate forms* which will settle and the two tubes can be compared in half an hour's time Any gross deficiency will be obvious

Tanret Mayer test for quinine in urine —The reagent is made as follows — Add a solution of 1.45 grammes of mercuric chloride in 80 c cm of undistilled water to a *solution of 5 grammes of potassium iodide in 20 c cm of distilled water* agitating the solution all the time To test the urine first boil and then filter it then add a few drops of reagent to 5 c cm of the urine an immediate precipitate forms if the alkaloid quinine is being excreted in the urine

Test for atebrin in the urine —Add 2.5 c cm of 60 per cent NaOH and 25 c cm of ether to 50 c cm of urine shake well allow the ether to separate pipette it off and to it add 5 c cm of N/10 hydrochloric acid The intensity of the yellow colour will be in proportion to the atebrin content of the urine

The question of administration of anti-malarial drugs by routes other than *via* the mouth can now be discussed

Parenteral therapy —There are two routes by which anti malarial drugs can be given parenterally (παρα = besides, εντερον = intestine), namely the intramuscular and the intravenous, we will consider them together first

The points for and against these methods of administration may be considered under the following headings :—

(i) *Necessity*—In certain circumstances parenteral therapy is *essential as for example in unconscious patients and in cases* where there is persistent vomiting

[illegible] —The main advantages are that one gives the ... as been taken, and *further* ... laimed by some workers,

(iii) *Dangers*—These are not very great *provided* sufficient care is taken Intramuscular injections require scrupulous asepsis, and great care must be taken to avoid large nerves or neuritis or paralyses may be caused

In intravenous therapy, the injections must be given *very* slowly and the drug must be well diluted, or syncope and collapse may occur

(iv) *Abuses*—To give parenteral injections as a routine measure in the treatment of malaria is unnecessary and therefore a definite abuse

Even when parenteral therapy is indicated, it is seldom necessary to continue it beyond the first day, after this oral therapy can usually be instituted (*see* figure 22)

The intramuscular *versus* the intravenous route —On the subject of parenteral therapy, there are acute divergences of opinion in the ranks of the medical profession Extreme views

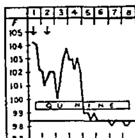


Figure 22 Malignant tertian malaria heavy infection with vomiting two intravenous injections of quinine

and for a number of years there has been an 'official' ban on intramuscular injections Textbooks, teachers, and even regulations have

dangers are all real though they may be very slight and the writer has seen both deaths and serious crippling result from intramuscular injections Nevertheless there are in the tropics many observant and careful practitioners who do not hesitate to give intramuscular injections of quinine whenever they think that parenteral administration is indicated

ioners does, intra-

The writer s own point of view is that only in one in a hundred cases of malaria is the parenteral route indicated, and where it is indicated the intravenous route is preferable ninety-nine times out of a hundred In the ten thousandth case he would not hesitate to give an intramuscular injection

Preparations and dosage —*Intravenous* —Ten grains of quinine dihydrobromide in 20 c cm of normal saline or 5 per cent glucose repeated about six ... in hydrochloride) ... Quinine must be g ... er minute *by the u a*

This is given into the gluteus maximus the vastus externus, the muscles at the angle of the scapula or the deltoid, or atebrin musonate 0.375 g (0.3 of atebrin hydrochloride) in 9 c cm of distilled water, into one of these muscles

* Urethane acts as an analgesic and also increases the solubility of the salt.

(4) **Treatment to prevent relapses** —The big-stick methods which were
loses of quinine over long periods, are no
The average case of malignant tertian
se after the *ordinary curative dose of* cinchona, quinine, or atebrin, but as relapse may be serious a second course after an interval of 7 to 10 days is usually advisable, the same remark applies to quartan infections In benign tertian infections the relapse rate after quinine alone is usually high (70 per cent) and some special measures should certainly be adopted

Following the line of thought started by Acton who showed that quinine acted best in an alkaline substratum, Sinton advocated the following routine procedure in the treatment of relapsing benign tertian malaria

The two mixtures he used were —

Mixture A		*Mixture B*	
℞ Sodii bicarbonatis	g lx	℞ Quininæ sulphatis	g x
Sodii citratis	g xl	Acidi citratis	g xx
Aquam ad	℥i	(or acidi sulph dil	xx)
		Aquam ad	℥i

Course —Give calomel in divided doses, *i e* 6 quarter-grain doses at half hour intervals at night, and magnesium sulphate at 6 o'clock in the morning, ℥ss to ℥i at 7-30, 9-30 and 11-30 a m give one dose of mixture A, followed by a dose of mixture B at 12 o'clock, at 6 o'clock give a dose of mixture A, followed half an hour later by a dose of mixture B

From the 2nd to 5th days inclusive give three times during the day a dose of mixture A, followed half an hour later by a dose of mixture B

On the 6th and 7th days give a dose of mixture A, followed half an hour later by one of mixture B, twice during the day

This makes a total dose of 180 grains of quinine Totaquina may be substituted for quinine without detriment to the treatment and where economy is to be considered this should always be done

Quinine *plus* plasmochin —A very marked further reduction in the relapse rate in benign tertian malaria can be obtained by the addition of plasmochin to the quinine The following dosages are recommended, the results obtained with each of these courses are about the same, but in either case the patients should be kept under observation for signs of intolerance to plasmochin

Plasmochin 0 02 gramme *plus* quinine 10 grains twice a day
or plasmochin 0 01 gramme *plus* quinine 10 grains thrice a day, for seven days

Atebrin and atebrin *plus* plasmochin *—Better results have been obtained with atebrin alone than with quinine alone, but, even with atebrin, plasmochin can be added with advantage in benign tertian infections

Atebrin 0 1 g thrice daily, plasmochin 0 02 g once a day for five days—given together or separately

There is considerable evidence to show that the combination of these two drugs enhances the toxic action of each, and patients should therefore

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*The writer has never seen any ill-effects from these combinations but recent experience of oth - than was previously suppo iter would therefore emphas he patient is under strict st iould only be used for the atment of relapsing benign en quinine is not available

be kept under strict observation while these combinations are being administered Many workers take t
alone for five days and then to giv
twice daily for another five days
danger of toxic symptoms is undoub
is prolonged

Arsenic is a valuable adjuvant in the treatment This can be given in the form of some arsphenamine preparation in three doses at 7 day intervals between two courses of cinchona febrifuge or quinine and alkalies, or as liquor arsenicalis added to a tonic mixture given after the specific anti malarial course

(5) **Gametocyte destruction in the cause of general prophylaxis** — This does not in any way help the patient for gametocytes can never again become asexual forms as long as they remain in the blood but if they are taken up by a mosquito they develop and the infection may be transmitted to others It is therefore only in the interests of *general* prophylaxis that attempts should be made to destroy gametocytes

It is in this capacity that plasmochin and the closely allied drug cilional are unique No other drug that we know will destroy the gametocytes of malignant tertian but this can be effected by a very small dose of plasmochin 0 01 gramme twice a day for three days It may be given for the last three days of the quinine or atebrin treatment or after the course has been finished

Mass treatment with plasmochin is a prophylactic measure suitable only in isolated communities but it is essential that every single member of the community particularly the infants should be treated and this is rarely possible (*see* p 112)

A comprehensive course —We have considered treatment of malaria under the five headings separately but in most circumstances one will

course should be given —

Quinine or totaquina gr x three times a day with plasmochin 0 02 gramme (or ⅓ grain) once a day for seven days followed by quinine or totaquina, gr x daily or 0.2 gramme atebrin in a single dose on two consecutive days each week in either case the last mentioned dosages must be given as long as prophylaxis is to be maintained

Recent experience —This has abundantly confirmed the value of atebrin in all circumstances in which quinine was used hitherto It has also tended to de emphasize the toxicity of atebrin

for five days—a total of 15 grammes (240 grains) in a week

For causal prophylaxis (suppressive treatment), the daily administration of 0 1 gramme of atebrin for six days a week is now favoured In order to reach the required blood level it must be given for two weeks before the subject enters the endemic area or alternatively an equivalent amount of atebrin must be given in a shorter period

malaria to prevent relapses is being questioned nowadays Although this subject must be *considered sub judice the routine use of plasmochin has been suspended in the American armed forces for the time being*

Much very important work on malaria has been carried out in Great Britain and America during the last few years but most of the results of this work are still considered of sufficient importance for the authorities in these two countries to prohibit their publication at present

Toxic Effects

The cinchona alkaloids —*Cinchonism* is the word used to indicate the mild toxic symptoms that follow the administration of these alkaloids namely headache and a 'fullness' of the head, buzzing in the ears, and deafness Cinchonism is largely responsible for the unpopularity of the cinchona alkaloids amongst patients The extent to which different individuals suffer from cinchonism varies very considerably, in this respect the personal factor is more important than the drug factor, though some alkaloids, *e g* cinchonidine, and some salts, *e g* quinine hydrobromide, are reputed to cause less cinchonism than others

Taken in large doses all these alkaloids have toxic actions, and even in moderate doses these effects may be apparent in susceptible individuals As we have noted above, quinidine is a heart depressant, and cinchonine is apt to irritate the gastric and intestinal mucosa and cause vomiting *and diarrhœa The other crystalline alkaloids may produce the same effects* but are much less likely to do so Quinine given in large doses produces

has also been reported in susceptible individuals

Finally, some individuals have an idiosyncrasy towards quinine and even a very minute dose of quinine will precipitate toxic symptoms, these include anaphylactic-like symptoms, urticaria and other rashes, local swellings, and hæmorrhages, as well as those already mentioned Such

fractional doses

case, this is another example of

In
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or five

the only drug of much
caffeine citrate, gr 4
mine is administered

Otherwise, symptomatic treatment is indicated, *e g* large doses of bicarbonate of soda or if necessary adrenaline for the vomiting

Plasmochin —The common mild toxic effects are cyanosis, gastric pains, slight jaundice, and more rarely hæmoglobinuria These were commonly experienced when the large therapeutic doses of 0 09 gramme

nmended, especially
ppears to have an
, there are however
follow small doses

The cyanosis results from the formation of methæmoglobin

There is still considerable misunderstanding amongst members of the medical profession regarding the place of plasmochin in malaria treatment, and instances of gross overdosage are not uncommon The following incident illustrates the dangers of self medication —

A planter living in a malarious district took a tablet of quino-plasmochin (containing 0 01 gramme of plasmochin) daily for two years as a prophylactic

Atebrin —Although toxic effects do occasionally follow atebrin administration, there is much misunderstanding on the subject

Almost
toxic Toxic
tered and th

that atebrin given in the ordinary therapeutic doses is not toxic to the ordinary individual, though occasionally a patient who has some idiosyncrasy to the drug will show special symptoms

This personal idiosyncrasy may be found with any drug but the practitioner naturally wants to know how often these susceptible individuals are likely to crop up in his practice

using a valuable drug At the Calcutta School of Tropical Medicine, though we have had patients who have come into hospital for treatment on account of suggestive symptoms following the administration both of atebrin and of plasmochin we have treated many hundreds of patients with atebrin during the last 10 years and in none of these have any serious symptoms followed

The actual and reputed by-effects can be classified as follows —

(i) *The result of a misconception, e g* yellow colour mistaken for jaundice

(ii) *Symptoms really due to malaria itself, e g* gastro-intestinal or cerebral disturbances, hæmoglobinuria

(iii) *Symptoms following overdosage*, as noted below in (iv) and (v) in—(a) patients who have undertaken treatment themselves, (b) patients who have been first treated by a doctor and then continued treatment themselves, and (c) patients whose doctors have wrongly advised them through ignorance

(iv) *Mild by-effects which cannot harm the patient but about which the doctor should warn him, e g* (a) yellow discoloration, particularly of the skin, distinguished from jaundice by relative freedom of the sclerotics, and (b) a 'knocked-out' *feeling (general lassitude) due to reduction in* hæmoglobin which is dependent on destruction of parasitized red cells (it does not occur in the uninfected person receiving atebrin)

(v) *Personal idiosyncrasy following ordinary dosage, e g* gastric pains, headaches, giddiness, anorexia, hæmoglobinuria, epileptiform fits, and psychosis

Hæmoglobinuria is more usually associated with plasmochin administration

not serious
complete
a series of
where an
The author
has seen only two instances in his personal experience

(vi) It is known that plasmochin in large doses will give rise to symptoms (*vide supra*), it is suggested that the addition of plasmochin in even small doses, increases the toxicity of atebrin

General management of a case—Malaria not being a disease of the modern metropolis but of the tropical jungle, recommendations to treat *it by putting the patient to bed in a high-ceilinged well-ventilated* room with a night and a day nurse in attendance may not seem very reasonable to the practitioner who has to treat the vast majority of his patients where *they lie, stand, or even march, and where the specific treatment will* be the only thing that he can possibly afford to consider Nevertheless, the message that such recommendations convey is the right one, namely, that *the potentialities for serious development of the malarial attack* should always be kept in mind, and that therefore the patient should, whenever possible, be put to bed and watched carefully for serious developments The room *should be darkened, and in the choice of clothing* and bedding the drenching sweats that the patient may suffer should be remembered If circumstances do not permit these to be changed frequently, then only *flannel clothing and woollen blankets should be allowed, on the other hand,* if proper *nursing is available these are unnecessary* and will not add to the patient's personal comfort

... the febrile period *only fluids should*
be g... bowels should be
kept ... omel at half-hour
inte... *subsequently* salts
in the morning when necessary Aspirin and caffeine can be given for headache, or, if these fail to relieve it, phenobarbitone

There is a popular theory that quinine should not be given at *the* height of the fever, there is no foundation for this, and specific treatment ... decided upon Unless
the blood examina
al was made of the

ing a regular dosage

If the patient has become at all anæmic during the attack—this is by no means always the case—the appropriate treatment should be given for the anæmia In the ordinary attack of malaria there has been no actual loss of iron from the body but nevertheless possibly because of previously existing iron deficiency so common in the tropics, iron given in large doses will usually improve the blood picture The rational treatment is with liver extract, either by injection or by the mouth and autolysed yeast products such as marmite In the absence of facilities for accurate blood examination, treatment for both microcytic, i e iron, and macrocytic anæmia, i e liver extract and marmite, should be given A useful prescription for the former is —

R Ferrous sulphate	grains 6		Liquor arsenicalis	minims 2
*Quinine sulphate	2		Dilute sulphuric acid	„ 5
Magnesium sulphate	„ 60		Peppermint water to one ounce	

To be taken three times a day

* Omit at present in interests of economy

The treatment of the special case —It is scarcely possible to lay down hard and fast rules and to provide for all contingencies in the treatment of any disease, and this is particularly true of malaria with its great variety

... Atebrin, in the form of the soluble atebrin musonate, is the drug of choice, this should be given intravenously in a dose of 0 125 gramme and repeated twice at one hour's intervals or intramuscularly as a single dose of 0 375 gramme (The large dose is often given intravenously, but a few instances of ill effects have been reported)

If atebrin, or its equivalent, is not available, the next choice is quinine, 10 grains (0 6 gramme) of some soluble salt dissolved in 20 c cm of saline and given intravenously Finally if for any reason (*e g* the absence of suitable syringe or of sufficient sterile solvent, or the difficulty of finding a suitable vein) the quinine cannot be given intravenously, it must be given intramuscularly, with the necessary precautions (*vide supra*) This dose should be repeated within a few hours if the acute symptoms do not subside

It is possible that the circumstances may necessitate the parenteral route being used on the following day, for example, if vomiting occurs or persists, but by the third day it will, in almost every case, be possible to change to oral administration This should be done at the earliest possible moment and the usual course completed

Chronic m

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infections, the

results

Another method for reducing the size of the spleen is the intramuscular injection of sterile fat-free milk, at least 12 injections, from 2 c cm to 10 c cm, twice weekly

The pregnant woman —The importance of giving the pregnant woman adequate treatment cannot be over-emphasized Whenever possible it is

PROGNOSIS

This must be considered from a number of different points of view, the immediate response to treatment, the chances of relapse, the immediate *mortality, the indirect mortality, and the general effect* on the health of the individual

Prognosis will depend on the species and strain of parasite, the nutrition of the patient and his previous experience of malaria, the treatment given, and complications

There … differences in the virulence of the malaria strains in … can be applied, but in peninsular Indi… ow virulence, whereas in the Himalaya… re virulent The first attack … and the seriousness usually

When treatment is immediately available no one should die as the result of malaria alone but when a patient is first seen already unconscious his chances of recovery will be in the inverse ratio to the length of time that he has been unconscious and of the further delay in administering treatment

In the partially immune adequate treatment will usually control the attack within

a single tertia

immune it

paroxysms

or five days (*see* figure 16) if the fever lasts longer than five days the efficacy of the treatment should be investigated (*see* p 101) and/or the diagnosis reviewed

The highest rate of immediate mortality is caused by *P falciparum* (malignant tertian) infection it is particularly fatal in the infant and young child and in the pregnant woman *P vivax* (benign tertian) and to a less extent *P malariæ* (quartan) infections will seldom prove immediately fatal even when no treatment is given

On the other hand relapses after adequate treatment are less common in malignant tertian malaria

Benign tertian malaria is probably little short of malignant tertian in the seriousness of its indirect effects especially on account of its marked tendency to relapse about 70 per cent of primary attacks relapse after an ordinary course of quinine

Quartan infections fall between malignant and benign tertian both in the severity of the attack and in the liability to relapse Kidney complications are said to be most common in quartan malaria but they also occur in malignant tertian

Anæmia is more likely to follow *P falciparum* infections The failure of the blood picture to return to normal rapidly is usually an indication that

expected However

extract will often be

though the infection

In a healthy well nourished person who receives adequate treatment convalescence is short and return to full activity may be expected within a week or ten days should frequent attacks or relapses occur at short intervals the period of convalescence will be considerably lengthened and still further so if the attacks are complicated by any bowel disease that interferes with nutrition

P ovale infections are always mild and seldom relapse

PREVENTION

To appreciate the possibilities of malarial prophylaxis the reader must turn back to page 64 and consider the factors that determine malaria incidence If the cycle can be broken or even sufficiently weakened at any point malaria will be prevented

The methods by which the cycle may be broken can be discussed under the same four headings —

A *The malaria parasite*
B *The mosquito vector*
C *Man*
D *The links between B and C*

A The malaria parasite—In theory, the malaria parasite might be attacked (i) in the mosquito, or (ii) in man, we will consider how far it is possible to translate this into practice

(i) It is conceivable that, without destroying the mosquitoes, by the alteration of the local vegetation on which they feed, the mosquitoes' (non-blood) food might be made to affect adversely the malaria parasite in the insects' gut Some worl
suggested that coumarin
has been experimentally
a suggestion has been m
the development of the

This theoretical method of malaria control has a popular appeal which opportunist scientists readily take advantage of to intrigue non medical administrators, and much valuable time is wasted in refuting unscientifically based claims, so far all work on these lines has been entirely without result

(ii) In man the parasite can be destroyed by means of drugs at any but the *sporozoite stage*

Drug prophylaxis may be considered under two headings, *individual* and *community*

The question of individual prophylaxis has been discussed above (p 100) and it has been shown that clinical prophylaxis can be achieved but *not true causal prophylaxis*

The

and in time those in the
itually this treatment will lead
much mischief will meanwhile
of malaria control it is useless

On the other hand, the plasmochin group of drugs have a direct effect on the gametocytes and even a small dose of plasmochin, such as 0 01 g twice daily for three days, will destroy the gametocytes or at least make them non-viable But if the patient still has an active infection, more gametocytes will be formed, so it is necessary first to destroy the parasites of the asexual cycle *by treatment with cinchona or atebrin and then to* destroy the gametocytes by means of plasmochin

The circumsta ... likely to
be completely effe ... a
mixed community ...
cyte producers, an ... e
of any scheme of treatment For a scheme to be a complete success ... y *single individual must be treated* Again, the community should be an isolated one, and new arrivals should *be subjected to treatment before* they are allowed to reside with the established community

Drug prophylaxis is expensive, both in cost of the drug and in the labour involved A 'blanket' treatment of the whole community will have

to be carried out, at first at frequent intervals The results will not be immediately apparent for at the commencement of the scheme the mosquitoes that are going to produce the human infections or re infections during the next month or so are already infected Later it will be possible to reduce the frequency of the blanket treatments, but the treatment of all those who suffer from an attack of malaria or who show gametocytes in their blood must be continued

Therefore before a scheme of drug prophylaxis is undertaken one should be satisfied that (i) no other method of prophylaxis is practicable in the circumstances (ii) the community is sufficiently isolated (a) geographically to ensure that there will be no infiltration of infected mosquitoes from outside and (b) socially to make it possible to prevent casual night visitors and to control permanent immigrants (iii) it will be possible to bring every man woman and child living within the locality into the operation of the scheme (iv) the cost for the continuance of the measure can be met from the funds available and (v) if complete success is achieved the results will be worth this cost

Whilst the occasions on which it will be worth carrying out a full

c

s

p

p

attack of malaria amongst the inmates or servants the blood is cleared of gametocytes, and that new arrivals from malarious places are subjected to a routine course of treatment The greatest danger is from servants and their children

In conjunction with other anti malarial schemes it is always worth giving plasmochin and some workers have advocated a modified form of 'blanket' treatment in conjunction with anti mosquito measures but it is very doubtful if in most circumstances the results are worth the additional cost of such a measure

On th other hand

Anti larval measures —The methods adopted can be discussed under the following headings —

(i) *Elimination of unnecessary collections of water*, these will mostly

tanks wells, and ditches and around hydrants and water taps

ction of man made breeding places, railways are the classical example which engineers make unnecessary

(iii) *The control of treatment of necessary local water collections*, of these common examples are cisterns wells fire buckets and fountains and ornamental water

(iv) *The elimination or treatment of large scale but avoidable collections of water* these may be due to water logging natural or brought

about by interference with natural drainage by the building of railways roads, etc, or may consist of irregular collections of water in dead rivers or in river beds during the drier seasons of the year

(v) *The control of larval breeding in large essential collections of water*, lakes, reservoirs and tanks, rivers, irrigation channels and streams drainage channels, and rice fields

In the case of water collections of the first three groups it is not

of mosquito
reasons, be-
carry other

diseases and are at the least a cause of annoyance to man The methods of dealing with these will usually be obvious Where they cannot be eliminated, they should be dealt with in other ways, wells and cisterns must, for example, be kept covered, or the water emptied periodically, in many cantonments in India, a 'dry day' is instituted once a week, on this day all uncovered collections of water must be emptied

Water collections of the last two groups present the real problems o malaria control by anti-larval measures about which so much has been written, it will only be possible here to enumerate some of the methods that have been adopted, and readers must refer to the many useful books on this subject for details (e g *Covell*, 1941)

The methods of eliminating the large collections of water or controlling breeding in them are almost without exception expensive, and it is therefore first essential to make sure that these potential breeding places

dissecting a large number of mosquitoes at the right time of year This common sense procedure of utilizing accumulated knowledge, to which has been added the results of local investigation, regarding which mosquito

malaria, on the tenth occasion it may make conditions ...

another vector and thereby defeat one's object This is where the expert's superior knowledge will come in, but where nature is concerned no one is omniscient

For some of the very worst set-backs in anti-malaria campaigns, the

have come to a new
or listening to the
to apply methods

that they had previously employed with success in other countries It is therefore essential to make a very careful study of local conditions before giving any advice on larval control methods Each country in the world presents its own particular problems, and if one cannot learn from some

of the books or papers
useful books in which

There are numerous methods of draining unnecessary collections of water, and circumstances will dictate which of these is likely to be the most fruitful Or it may be cheaper to treat the breeding places with larvicides

the rate of flow intermittent irrigation flooding periodic sluicing or varying the water level shading or letting in the light by biological means *e g* changing the flora and fauna introducing larvivorous fish or deterrent aquatic vegetation (largely theoretical) or by poisoning the larvæ or their food supply, with oil chemical poisons *e g* DDT paris green or copper sulphate or vegetable larvicides *e g* pyrethrum or derris

Anti imago measures—The principle of this method of control is not simply to reduce the number of mosquitoes nor even to kill the infective mosquitoes but to *prevent the local malaria vector from becoming infective by shortening its average duration of life* The most striking demonstration of its effectiveness is that in all cases when spraying is carried out properly the infectivity rate among mosquitoes immediately drops to *nil*

Recently much more attention has been paid to this method particularly in Europe and cooler countries where the mosquito enters a house and tends to remain there for long periods if left undisturbed and where it is much easier in closed rooms to destroy them However this method has been used extensively in hotter climates even under conditions where it is more difficult to close the rooms on account of the much more open nature of the habitations and considerable success has been claimed It is particularly applicable to private houses barracks and offices but can be applied to the huts of the poorer inhabitants It is also employed usefully in public conveyances railway carriages omnibuses and aeroplanes

The methods of destruction employed are swatting trapping fumigating and spraying the last named usually being the method of choice

Spray killing of adult mosquitoes is now recognized to be one of the major methods of control in anti malaria campaigns It is the only one of the anti imago measures of real practical importance It is the only measure which can have an *immediate* effect on the course of a malaria epidemic which has already started it is the only anti malaria

troops operating under modern war conditions

Covell considers that the Punjab epidemics provide an excellent

sprayers to meet an emergency

The most effective sprays have a basis of kerosene and the majority contain pyrethrum there are many proprietary brands but a useful and not expensive spray may be made from 19 parts of kerosene and one part of concentrated (2 per cent) extract of pyrethrum

There are certain advantages in a spray with a watery base; the [illegible]

[illegible] Rao (1942) have recommended the following spray :—

> Twenty pounds of pyrethrum flowers are extracted with 12 gallons of white kerosene This will make 10 to 11 gallons of concentrated extract, the extract is mixed with water in the *proportions of 1 to 7, and* 23 *grammes of* sodium lauryl sulphate (or 'Gardinol') are added for each gallon of emulsion

Technique of Spraying

All apertures should be closed as far as possible before spraying, and should remain closed for 20 minutes thereafter It is, however, usually impossible to do this completely, in which case it is necessary to use rather more of the spraying solution It is more economical in the end to use a greater quantity of spray, rather than to waste time in stopping up apertures with sacking, etc Even when the structure sprayed consists of a thatched roof without sides, numbers of mosquitoes can be killed by directing the spray upwards into the thatch Before spraying the inside of a hut, the outside should be systematically sprayed under the eaves The sprayer should in all cases be directed upwards

Period of spraying —Systematic spraying should commence a fortnight before the malaria season is expected to start and should be continued throughout the transmission period

Time of spraying —Mosquitoes almost invariably feed during the night *A. minimus*, for instance, usually feeds between midnight and daybreak After feeding, the mosquito remains in a sluggish condition during the early stage of digestion of its blood meal It is therefore advisable to commence spraying in the early morning as soon as after daybreak as possible

Frequency of spraying —The efficacy of the method is in direct proportion to the frequency with [illegible] among the vector spec[illegible] by spraying once a we[illegible] rate among the local [illegible] preferably thrice, a we[illegible] to spray as often as possible

Amount of spray required —*This is about half an ounce per* 1,000 cubic feet, which is about the size of the average one-roomed coolie hut Allowance must also be made for spraying other suitable anopheline shelters, such as cattle-sheds and store-rooms

Sprayers —Power-driven sprayers are the most effective, and are also the most economical in consumption of spray, in labour and in time of spraying The apparatus used is identical with that employed for the spray painting of motor cars, etc The following models have been found suitable :—

1 De Vilbiss portable petrol-driven power sprayer, type NH-616, 1/ H.P., mounted on trolley, cost about Rs 605/-

2 De Vilbiss portable electric (universal) sprayer, type NC-615, 1/4 H.P., mounted on trolley, cost about Rs 330/-

Excellent results can also be obtained by the use of hand sprayers although there is no type at present available which is at the same time effective in *operation durable*, easy to operate, and economical in consumption of spray

Freon aerosol "bombs"

These are small hand-grenade-like metal containers in which there is a mixture of pyrethrins—1 per cent sesame oil—2 per cent, freon (dichlor-difluoro-methane)—97 per cent Since the vapour pressure of the freon provides the necessary spraying power it is only necessary to remove the cap to operate the spray Freon is itself [illegible] and [illegible]

It seems possible that DDT
Pyrethrum will grow in ma
flowers have been found to gi
flowers, though not as high as

There are probably unexplored biological methods of destroying adult

was found, did not feed on mosquitoes

C *Man*—The elimination of man would break the malaria cycle Short of this drastic procedure, it is however possible to take some action under this heading

Increasing immunity—Immunity is seldom complete, but if a community is by previous experience of malaria well immunized against a particular strain—the term *salted* is used in this connection—it will mean that the adult in the community seldom suffers from an infection heavy enough to cause a febrile reaction or to lead to the formation of any considerable number of gametocytes, he will thus not himself become a casualty nor will he be a prolific source of infection to the mosquitoes in the locality In this way, immunity acts as a brake on the intensity of the malaria incidence in any community and any measure that raises this immunity is an anti-malarial measure, just as, conversely, anything that lowers it is a malariogenic factor

A method of malaria control

(see figure 23)

Other measures of control under this heading will include the careful selection of labour forces so that immune populations are not mixed with non immune, and children are excluded as far as possible

The question of employment of *salted* labour is a very complicated one Some employers of labour advocate it strongly and others criticize it The ideal labour force in a



Figure 23 Decrease in mortality from malaria in Italy over a forty year period (Hackett 1937)

D *The links between the mosquito (B) and man (C)*
that the mosquito ve
occur The methods
may be considered ur

General—In the choice of sites of towns, villages, settlements, coolie lines, camps or even houses, the question of the proximity to uncontrollable mosquito-breeding grounds, as well as to uncontrollable human reservoirs of infection, should always be considered Whenever possible the opinion of an expert malariologist should be obtained In the past, millions of pounds could have been saved by this simple precaution, and mistakes are still being made Unless he has made a special study of malariology and had some personal experience, a medical officer should refuse to express an opinion on a matter of this kind, and, whenever any considerable amount of money is involved, he will be well advised in any case to insist on the opinion of an expert malariologist being obtained

Small bodies of men, hunting parties, prospectors and engineers, o 'commando' troops, going into malaria infected country should be warne to avoid native villages for their temporary night halts as they would a plague-stricken village, they should also view with equal suspicion an clearing in bush or jungle which has obviously recently been the site o an encampment

Where the village or residence is already established there are som biological methods of interception that have been advocated, these includ the planting of alleged deterrent vegetation, *e g* neem and eucalyptus trees, castor-oil plants, lavender and clover, and the use of cattle to deviate the attentions of the mosquitoes from their human sources of blood supply *i e* zoopiophylaxis (*see* p 70 Zoophilism) In practice, all these biological methods have proved disappointing

Another measure is the **screening** of barracks, hospitals, and houses In some countries this is practised extensively and its popularity is increasing, it must always be considered, whenever it is practicable, as an additional measure Dr D P Curry, who has directed the mosquito control work for many years in the Panama Canal Zone, recently wrote, 'in spite of all our sanitation, we still must insist on screened living quarters, and screened offices for those persons who must work at night' It does not add much to the cost of a building to include screening in its construction Combined with systematic spray-killing, screening may be considered a major method, in places where more comprehensive methods of malaria prevention are impracticable It is however necessary that

this reason the method
most generally useful,
0 gauge (S W G), this
eep out all mosquitoes

in ordinary circumstances and does not interfere too much with the entrance of fresh air

buildings are the avoidance of dark
during the day and the provision of
erging on the personal methods of

prevention

The **personal** methods of protection include the use of repellents for smearing over the uncovered parts c ... with one of mosquito killing sprays (*v* ... mpler means of protecting the legs *e g* a ... whilst sitting at table, veils and gloves, and mosquito nets

Innumerable **repellents** have been suggested from time to time but in India pyrethrum was preferred before the introduction of the new insecticide, DDT which will probably prove cheaper

Covell recommends the following formula —Extract of pyrethrum (2 per cent) 20 c cm Oil of citronella 5 c cm Gum tragacanth powder 4 grammes Water 80 c cm

Note—If a stronger extract of pyrethrum can be obtained it should be used If the European tragacanth is available the quantity should be 5 to 6 grammes

A great improvement has recently been made in repellents and some of the best in use today are effective for 24 hours with one application

— L — h do

Mosquito nets should be 25/26 mesh of 30/s cotton These trade terms will mean little to the ordinary man they are arrived at by fantastic methods of calculation with which the reader need not burden his memory They do *not* mean that there are 25 holes to the inch linear or square actually a net of this specification has about 12 holes to the linear inch and 150 to the square inch

Similarly the mosquitoes must be prevented from feeding on an infected person and in a hospital or other institution the patient suffering from malaria should always be made to use a mosquito net as a measure of protection for the community

Amelioration of the effects of malaria —*In certain circumstances it* has been found that the practical difficulties of preventing malaria are so great that preventive measures are scarcely worth attempting In these circumstances the question of organized treatment to ameliorate the effects of malaria should be considered Bonification referred to above is really a measure of this nature though it may achieve mosquito control as a side line

In many places in India there is little hope of eradicating malaria and the next best measure is to provide cheap or free treatment for the individual sufferer not with any hope of actually eradicating the disease but in order to mitigate the damage that the infection does This is especially true in the epidemic areas in the Punjab where for a short time during the year conditions may be extremely favourable for transmission and where anti larval measures would be impossible or prohibitively costly By studying climatic conditions that precede these epidemics sanitarians have learnt to foretell epidemics and with the help of special epidemic units, now arrange for the mass treatment of the population by free distribution of cinchona alkaloids and by other means The possibilities of combining this treatment campaign with spray killing of mosquitoes is discussed above

M r c D r d *recommending any procedure* de that one should have all the ob arly every case some form of ma n By a malaria survey one ascertains the extent to which malaria is present in the locality or if a large area is involved in different parts of that area how it affects different sections of the population the time of year when it is most prevalent what are the vectors what are their sporozoite rates and where they breed and in fact all that can be ascertained about the epidemiology of malaria under the various headings under which it has been discussed above

The extent of malarial endemicity can be judged from the '*parasite rate*' or the 'spleen rate', or preferably both To find out the parasite rate, thick and thin films will have to be taken of a representative group of the population, and examined by the methods described above, from this *examination the infestation rate* and the average parasite count can be calculated, of the whole and of different groups of the population, but there are many refinements in this type of work and the reader is referred to one of the books devoted to this subject (*e g* Covell, 1939)

The calculation of the **spleen rate** has similarly been reduced to a fine art (Covell*, ... that give invaluable *information* ... *children between the* ages of two a ... between these years the spleen's reaction to malarial infection is more constant than at other ages The children should be lined up against a wall and the sizes of their spleens ascertained by palpation The children are placed in five classes according to the sizes of their spleens, class I, not palpable—o, class II palpable but not beyond the costal margin—p, class III, up to three- ... this but ... —+++ ... enlarge ... oncerned, ... rate, as follows —

Healthy areas—below 10 per cent
Areas of moderate endemicity—from 10 to 25 per cent
Areas of high endemicity—between 25 and 50 per cent
Areas of hyperendemicity—*constantly* 50 per cent or over

In conclusion the successful control of malaria requires a very wide ...

is decided upon The ex ... should never be ignored, ... that the methods have n ...

The economic aspect will always be paramount in this imperfect world One's first thoughts must be, how much will it cost and will it pay? An accurate answer to the first half of the question should be given, but for the second a long view ma ... should be satisfied with a promising l ... years before the good effects a ... pects a quicker return though they may be content to wait a year or two, but on the other hand, a commander of an army, or an engineer in charge of the construction of a railway, road or bridge, may have little interest in what happens next year and only be concerned with next week or next month

* Christopher's method has many advantages, including the important one of allowing for differences in the size of the children and is very easy in practice though from the description it appears complicated It consists in marking the 'apex' of the ... the umbilicus-apex ... om a table ... *lth Bulletin*

MALARIA THERAPY

The origin of this form of treatment was the observation that though syphilis is as common in most malarious countries as it is in the temperate zones neuro-

This form of treatment attracted a very great deal of attention in Europe and in England a mosquito farm was organized under the auspices of the Ministry of Health for the purpose of conveying malaria infection easily and safely to those who were to be treated by this measure

Besides being a very successful form of treatment—about half the patients suffering from general paralysis thus treated were considerably improved by the treatment—it provided us with a very valuable opportunity for studying experimentally certain aspects of malaria transmission and treatment The most important workers in this field have been James and later Sinton in England Ciuca in Roumania and Boyd and later Shannon in the United States

The infection may be transmitted by the agency of laboratory bred mosquitoes directly by their bite or by dissecting out the salivary glands and inoculating the sporozoites or by the injection of infected blood (*see* p 71) In the latter case 2 to 5 c.cm of defibrinated blood from a patient with malaria is inoculated intra

produced the incubation period of inoculation malaria is shorter the course tends to be milder there are fewer early and no late relapses and it is much more easily controlled by treatment

the species

An example of this difficulty occurred recently in the author s experience

carried out a few more quartan parasites were found but the infection was still mainly benign tertian As the infection was showing signs of dying out inoculation was not delayed further Twelve days after the inoculation the tabetic patient developed fever which was found to be due to a heavy *malignant tertian* infection and within a day or two very energetic anti malarial treatment had to be given to save his life

The patient should be allowed to have 8 to 12 paroxysms before the infection is terminated by anti malarial treatment If the rigors are too severe and occur

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BLACKWATER FEVER

Definition —Blackwater fever is a special manifestation of malaria, characterized by hæmoglobinuria

The pathology and the clinical picture in this condition are so characteristic and so different from those of the ordinary malarial attack that it is justifiable to consider it as a separate disease entity, though it is now generally accepted that plasmodia are the sole causal organisms

Historical —The main historical interest is that although malaria has been known for twenty-five centuries, with the exception of some doubtful references in Hippocratic medical writings there is no reference to the blackwater syndrome in medical literature until a little over a century ago, when Boyle (1831) referred to it in his *Fevers of West Africa* Scott (1939) draws attention to the fact that the literature of blackwater fever has shown a marked national grouping, about the middle of the century, writers reported the disease in Madagascar and in other French possessions in Africa, after another decade the Greeks took up the subject, and these are followed in turn by Italian, American, Dutch (Java), German (1890) and eventually British medical writers

This late historical appearance of the disease has been used to support various claims regarding its ætiology, for example that it must be a disease *sui generis* or at least caused by a special plasmodial strain and alternately that it must be du . eral use about the time of the a In view of our knowledge of the present writer that the incre last century was associated with the widespread foreign invasion of tropical territory that occurred at this time and that beyond this the observation does not point to any special ætiological factor

EPIDEMIOLOGY

Blackwater fever occurs only in highly endemic malarious countries (or amongst persons who have lived in such countries) and its seasonal incidence is always correlated with the season of highest malaria incidence, so that its epidemiology is the epidemiology of malaria, with some special features

Geographical distribution —As it occurs in nearly all the intensely malarious countries in the world, no separate map is necessary, it does not however, occur further north than 40°N or further south than 20°S In Europe it is most prevalent in Greece and Macedonia and in so them

In India, the worst blackwater fever areas are in the Dooars and Terai (at the foot of the Himalayas), Assam, the Chittagong hill tracts, Santal Parganas, Chota Nagpur, and the Madras Presidency, and in Burma in the North and South Shan States

Whilst these are the localities where the patient acquires his predisposing tendency to blackwater fever, the attack may develop in some non-malarious country, it is quite common, for example for those returning from the East to be attacked in London

Local distribution —It occurs mainly in areas where malignant tertian malaria is endemic throughout the year In India, and in many other countries, it is prevalent where more civilized races come into close contact with primitive peoples, that is to say, on the borders of jungle tracts In places it also has a local distribution that does not seem to be solely explained by high malaria endemicity, for in other equally malarious districts it does not occur, this
local carrier species of mosqu
which endows it with special

Individual incidence —In blackwater fever areas, the disease is very rare amongst the local natives, but occurs amongst foreigners, in India, it lom occurs area, and who have had a previous attack

People of all ages and both sexes may be attacked

ÆTIOLOGY

The ætiological factors must be considered under two headings, (*A*) *predisposing*, and (*B*) *precipitating*

Of the predisposing factors, (*i*), (*ii*) and (*iii*) are essential, and (*iv*) and (*v*) important additional factors The incidents that may precipitate an attack can be placed in three groups, one alone is sufficient but there may be a combination of precipitating factors

(*A*) *Predisposing factors* —(*i*) A plasmodial infection is the first essential The disease is nearly always associated with malignant tertian infections, but instances have been reported where apparently pure benign tertian or pure quartan infections have given rise to blackwater fever

(*ii*) Absence of established immunity to all local malaria strains, such as is acquired by indigenous inhabitants of a locality

(*iii*) Previous subjection to intense malarial infection over a period of at least a year

(*iv*) Irregular and inadequate treatment of these attacks

(*v*) A previous attack of blackwater fever, this is evidence of individual susceptibility for about 10 per cent of blackwater fever subjects suffer a second attack

(*B*) *Precipitating factors* —(*i*) Quinine administration this has a double action as it stimulates the action of the reticulo-endothelial cells to destroy parasites and incidentally red cells, and quinine itself, especially as an acid salt also has a slight hæmolytic action The other anti malarial drugs may act in the same way, but are not so frequently reported as the precipitating factor, possibly because, as in the case of atebrin the main action of the drug is a direct one on the malaria parasite itself

(*ii*) Cold (*cf* paroxysmal hæmoglobinuria), fatigue (increase of sarcolactic acid), alcohol, arsphenamine and certain other toxic drugs, and trauma

(*iii*) *X*-ray applications to the spleen, which stimulate the hæmolytic cells of the reticulo endothelial system

The mechanism of hæmolysis —The exact physiological process by which old and worn out red cells are removed from the circulation is a question not yet finally settled, but it is probably an intracellular, rather
be found
ı malarial
debris is
iti bodies
heir part
-y large
blood
up the
luction,
respond
oclastic
be brought
a new strain
or, even in
e, which, we
subjection to

cold which assists the action of the hæmolysin already formed (cf paroxysmal hæmoglobinuria)

(bilirubinuria)

Theories regarding the cause of blackwater fever—Even if we accept the description given above as the mechanism of the attack it does not really explain why it occurs in some people and not in others One sugges-

but against it is the occurrence of blackwater fever in therapeutic malaria—a few instances of which have been reported—where the virulence of the strain used is known The alternative suggestion, that a benign strain

Some years ago the writer tentatively put forward two suggestions these were based on both epidemiological and experimental evidence (Napier and Campbell 1932) The first was that rapid passage through a series of susceptible hosts raised the virulence of a previously normal strain of malaria parasite and the second somewhat contradictory to the first that the virulent strains of plasmodium which are harboured by the immunized people of jungle tracts when transmitted to non immunes (non immune to that particular strain) caused a virulent infection In the experiments on which these theories were based by passage of the Simian plasmodium *Plasmodium knowlesi* (later named as such) from a monkey of the *Silenus irus* species in which it was dormant and over shadowed by a *P inui* infection through a series of *Silenus rhesus* monkeys we produced a virulent infection associated with hæmoglobinuria* in the latter species (and incidentally drew the first attention to this plasmodium species which has played such an important role in experimental malaria ever since)

There is little support for the former theory but the latter dovetails in with the general theory enunciated above

Other theories that have been put forward have either been disproved or died through lack of support These include the theory that it is the result of acidosis enhanced by giving acid salts of quinine, or the excessive formation of sarco lactic acid by muscular exertion, this theory is weakened by the observation that acidosis is not constantly present in blackwater fever That it is a pure quinine intoxication has now been disproved by the occurrence of blackwater fever in people who have not taken quinine so frequently that this theory can have few supporters The finding of

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*This hæmoglobinuria is not strictly comparable to blackwater fever as it is not associated with any hæmoclast c crisis but is simply the result of excessive destruc tion of red cells by the plasmodium infection possibly combined with a low kidney threshold for hæmoglobin in the host

a spirochætal infection in blackwater by one or two observers has not been confirmed, nor has any other specific organism been found, though there are some who still consider that it is a disease *sui generis*

In the writer's opinion the 'phenomenon' of blackwater fever requires *no explanation beyond that already outlined* in the previous paragraphs, if allowance is made for varying individual susceptibility

PATHOLOGY

Morbid anatomy This is basically the same as that of malaria, but
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In blackwater fever, the most characteristic and extensive changes are in the kidneys The free hæmoglobin in the blood passes through the glomeruli and reaches the tubules where, the environment being more on the acid side, acid hæmatin is precipitated, and the tubules become blocked

The kidneys are large and dark, the tubules are blocked with brown debris and hæmoglobin casts, and there is cloudy swelling and degeneration of the tubular endothelium The liver is stained an intense yellow (hæmosiderin), and there is central necrosis of the parenchyma cells The gall-bladder is filled with thick viscid bile The spleen is enlarged and almost black (hæmozoin pigment) on section, there is general endothelial proliferation and there are areas of focal necrosis in the malpighian corpuscles

Blood —Th
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The anæmia ma
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anæmia is usual

Parasites are by no means always found in the peripheral blood at the time the patient comes under observation, but an investigation in
blood in 73 per cent
he day of the

In a series of 20 cases in northern Bengal, Bhattacharya (1941) reported finding parasites in the blood in six out of ten cases in which there had been no previous quinine treatment

Biochemi
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the blood (Fairley, 1941)

There is marked hyperbilirubinæmia in severe cases, the indirect van den Bergh test indicating an amount as high as 40 mg per 100 c cm of *blood*

The blood urea rises as high as 450 mg even in non-fatal cases and in cases of renal failure this may be higher The cholesterol content of the blood is considerably reduced The alkali reserve may be as low as 30 c cm CO_2

level
of the
col and
eve ivers
the colour of the urine lightens to a light brown and finally a yellow, which may persist in the urine for many days The urine is markedly acid If it is shaken, the presence of hæmoglobin is shown by a pink foam

The test for albumin shows a heavy cloud

In severe cases bile is present but this is usually masked by the hæmoglobin Methæmalbumin is not excreted by the kidneys and does not therefore appear in the urine

Microscopically, there is much brown debris and hæmoglobin casts, but there are few red cells

The *fæces* may show pleocholia for a few days

SYMPTOMATOLOGY

Prodroma —Mild febrile attacks associated with a yellow discoloration of the sclerotics or frank jaundice are sometimes noticed for a day or so before the real attack, but as a rule the onset occurs with dramatic suddenness

Onset —Sometimes the first sign of the disease is that the patient finds his urine bright red, usually, however, the syndrome supervenes during an apparently ordinary attack of malignant tertian malaria, there is headache, very severe prostration with pain in the kidney region, nausea, and vomiting, and then the patient notices that his urine is coloured red

Bhattacharya (*loc cit*) reported the first appearance of hæmoglobin in his 20 cases as follows —

Day of fever	No of cases	Day of fever	No of cases
1st day	3	4th day	5
2nd day	3	5th day	2
3rd day	7	TOTAL	20

The course of the disease —There is usually a single severe hæmoclastic explosion, all the damage being done in a matter of a few hours, but there may be a series of hæmolytic crises, in which case the prognosis is poor The temperature is high at first but tends to be very irregular later, the pulse is very rapid, and the blood pressure is low, later, the blood pressure may rise with the onset of renal failure The headache, na
continue
may be ma
lessness and
thready pulse

Meanwhile the urine will have passed through the stages of port-wine colour and be almost black but in severe cases anuria will set in, and,

though it is not uncommon for urinary secretion to commence again, even after 48 hours, azotæmia ('uræmia') as the result of continued anuria is a common cause of death Even polyuric cases may prove fatal

The spleen is usually markedly enlarged and tender (but may be temporarily reduced during an attack as a result of the expulsion of reserve blood), the liver is tender and the gall-bladder may be felt, jaundice appears early, on the second day, and is usually unaccompanied by itching

Recovery may be rapid, or on the other hand the symptoms may increase and the patient die of heart failure, or cerebral symptoms—irritability, delirium and coma—may appear, in such a case he usually shows early signs of collapse, the breathing becomes Cheyne-Stokes in character and death soon follows

A marked degree of anæmia, which is usually macrocytic, and general debility a
place very
definitely
infra)

Relapses are common

) the mild (more or-
(*c*) the continuous
anuric, and (*e*) the
hæmorrhagic

DIFFERENTIAL DIAGNOSIS

The conditions from which blackwater fever has to be distinguished can be grouped under the following headings —

(*a*) Hæmoglobinuria caused solely by the taking of quinine or plasmochin (the existence of this condition is now questioned), 'march' hæmoglobinuria, paroxysmal hæmoglobinuria (an interesting condition dependent on the incompatibility of an individual's plasma and red cells
itated by
chiafava-
aused by
and as a
etary substances, an example of
blackwater in other symptoms
(*Vicia faba*) in excess (Luisada,
1941)

Certain drugs and other substances may produce a red coloration in the urine, which could be mistaken for hæmoglobin, for example, beetroot, cochineal and, amongst the drugs, amidopyrin, phenolphthalein, and prontosil-rubrum

Hæmoglobinuria is also imitated as a means of malingering (in India, *pan*, commonly chewed by Indians, particularly women, added to the urine makes a fair semblance of hæmoglobinuria) The final test for hæmoglobin is by means of a spectroscope, the hæmoglobin bands are easily recognized This can be done with a pocket spectroscope

(*b*) Hæmaturia, due to various local causes, oxaluria, new growth, stone, etc , yellow fever, hæmorrhagic diathesis and other conditions where hæmorrhages occur from mucous membranes

(*c*) Jaundice, due to any cause but especially yellow fever, or Weil's disease, in both these conditions it develops later and tends to progress

TREATMENT

General principles —The patient should be treated and nursed on the
t warm and
losis should

bicarbonate as they report that it also helps to reduce hæmolysis

Anti-malarial drugs —In the majority of cases there are no parasites in the peripheral blood at the time the patient is seen after the attack, and in these circumstances no anti-malarial drug is necessary If parasites are still present atebrin in the usual doses (*see* p 101) should be given

Symptomatic —For anuria if intravenous therapy fails hot fomentations o
and fir
citrate
a few

Sodium sulphate, 1 89 per cent of the anhydrous salt in distilled water, given intravenously by the drip-feed method, up to a litre, should be tried, if the above methods fail

The diuretics that are most likely to be of value are caffeine and sodium benzoate given by intramuscular injection in doses of 4 grains or caffeine citrate gr iii or diuretin gr x three times daily given by the mouth

Vomiting can sometimes be stopped by giving the patient ice to suck, if not, 1 c cm of adrenaline diluted with an ounce of water should be given by mouth but if this and other simpler means of controlling vomiting fail, an injection of morphia (1/10 grain) and hyoscin (1/200 grain) may be given

For cardiac stimulation, camphor in oil cardiazol and coramine are the drugs of choice

As a purgative, calomel should be given in divided doses (¼ grain half-hourly up to 1½ grains)

'Specifics' —A large number of specifics for the treatment of blackwater fever have been advocated Many of these have acquired a considerable local

plant has been prepared which has been shown to possess definite anti-hæmolytic properties *in vitro* (Gupta *et al*, 1942)

Ano
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tried in

A line of treatment more recently introduced is with cortin, or its synthetic equivalent, desoxycorticosterone acetate, 25 mg immediately and 5 mg 4 hourly, combined with vitamin C in maximal doses intravenously or intramuscularly, and cholesterol 15 grains 4 hourly by the mouth. Even in this case, the exact rationale is not clear and it is doubtful if cholesterol taken by mouth increases the blood cholesterol appreciably, but the writer has seen uniformly satisfactory results with this routine during the last few years Again, however, no scientifically controlled series of experiments of sufficient number to carry any weight have been reported upon

Blood transfusion and other hæmatinic treatment —Transfusion has
been
It
it is
suffering from anoxæmia after a crisis, transfusions of cross matched whole blood up to 400 c cm in the first instance are certainly worth considering they must always be given slowly Oxygen will always be *helpful at this* juncture

actual loss of
ich should be
provement in
r some weeks
if possible

Diet —Diet should be fluid and of low nitrogen content during the acute

that have accompanied the attack

Convalescence —A special word of warning is necessary in convalescence, as sudden heart failure is common, some physicians insist on all patients remaining strictly in bed for at least 10 days after the hæmoglobinuria has completely stopped

PREVENTION

The prevention of blackwater fever is the prevention of malaria and the subject does not require separate discussion here *(see pp 111–119)*

The drug prophylaxis is also the same as for malaria but, in view of the undoubted action of quinine in precipitating an attack of blackwater fever, the question whether it is advisable to take prophylactic quinine in a blackwater fever area will naturally arise *Whenever this* point has been investigated it has been found that the disease is far less common amongst those who take prophylactic quinine regularly *than* amongst those who take it just when they happen to remember it or not at all Thorough treatment of the mal
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group of drugs

If the old remedy *Vitex peduncularis* lives up to its new promise it might provide a drug that could *usefully be employed prophylactically* in a blackwater fever country, especially by blackwater fever subjects, whenever they *feel a malarial attack coming* on

PROGNOSIS

One of the principal characteristics of blackwater fever is the great variability of the severity of the disease from place to place and from time to time in any one place this is why the results of any particular form of treatment are so likely to be misleading When large series are reported the death rate usually varies between 10 to 20 per cent but in a smaller series a death rate of 40 per cent is not at all uncommon and conversely death rates as low as 5 per cent are reported

The prognosis deteriorates with each successive attack There is a popular saying in blackwater fever districts that 'one often recovers from the first attack seldom from a second and never from a third This is of course not true but it conveys the right message and as there is some evidence of individual susceptibility which is possibly enhanced by an attack it is advisable for a blackwater fever subject to seek employment in some other locality

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Addendum—Recent examination of the current explanation for the anuria namely damage to the kidney as a result of excreting the large moleculed (68 000) hæmoglobin and precipitation of acid hæmatin in the

epithelium is far more sensitive than the glomeruli It is believed that acidosis which is not constant cannot alone explain the changes and that acid base electrolyte water balance must be considered as a whole dehydration extrinsic and intrinsic is an important factor

The practical point here is that treatment by excessive alkalinization may do more harm than good Whole blood transfusion has for many years been used successfully in treatment even when the degree of anæmia did not seem to demand it and though it is known that the hæmoglobin thus given is often hæmolyzed It seems possible that better results might be obtained with plasma transfusions combined with oxygen inhalation

LEISHMANIASIS

CLASSIFICATION OF LEISHMANIA INFECTIONS

The diseases in man caused by protozoa of the genus *Leishmania* Ross, 1903, can be considered under the following three headings :—

(*i*) Visceral leishmaniasis, or kala-azar, in which the causal organism, *Leishmania donovani*, is spread by the blood and invades practically all the tissues in the body except those of the nervous system

Ther[illegible]
organism [illegible]
generally [illegible]
Similarly [illegible]
variety c[illegible]
from *L* [illegible]

Post-kala-azar dermal leishmaniasis, in its numerous forms, is a late sequel to the generalized infection, in this condition the parasites (*L donovani*), having disappeared from the viscera, are confined to the skin and cause non-ulcerative skin lesions unaccompanied by any general symptoms

(*ii*) Cutaneous leishmaniasis or oriental sore, in which the infection is localized in the skin and causes ulcerative lesions, in this condition the infection is apparently not spread by the blood-stream, but, rarely, extension has occurred along lymphatic channels, *Leishmania tropica* is the causal organism

(*iii*) Muco cutaneous or South American leishmaniasis, or espundia in *which there is a primary invasion of the skin, as in* oriental sore, followed, sometimes after the original sore has healed, by a specific ulceration of the nasal, buccal, and pharyngeal mucous membranes, the spread of infection is presumably by the blood-stream, although the blood infection has not been demonstrated in this disease, *Leishmania brasiliensis* is the causal organism

KALA-AZAR

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The position was clarified when in 1903 the causal organism, now classified as
Leishmania donov ... Leishman in the
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the smears made

A disease known as 'ponos', which had been recognized in Greece and other Mediterranean countries for many years, was shown to be caused by the same organism

Kala-azar was first diagnosed in China by Aspland in 1910 and in the Sudan by Bousfield Thomson, and Marshall (1911)

EPIDEMIOLOGY

Geographical distribution —The disease has a widespread distribution in the Old World, and has been reported from South America, but up to now not from Oceania

In Europe the most he...
Italy, and certain Mediterr...
case has been reported in V...
be comparatively common
provinces of Catalonia and ...
and other Greek islands, isolated cases have been reported from many other Mediterranean ports At Catania 1,424 cases were diagnosed in a period of ten years, and in Hydra 39 per cent of the deaths among infants during one year were said to be due to this disease, but in most of the other places it is only sporadic in occurrence (*see* figure 24)



Figure 24 Map showing kala-azar distribution (shaded) in the Mediterranean area

In the Mediterranean area the disease is confined almost entirely to infants and young children

In **North Africa** the same infantile form of the disease occurs along the Mediterranean littoral, in Morocco, Algeria, and Tunis, the incidence being highest in the last-named There is another endemic area in the Sudan, in Kassala and the Blue Nile district, and cases have been reported from Abyssinia, northern Kenya, and a few other places in tropical

Africa, but only in the Sudan endemic focus has there been any serious incidence of the disease, here kala azar, which is not of the infantile type but has an age distribution comparable to the Asiatic form of the disease came into prominence during the fighting in 1940-41 in Abyssinia and on the borders of the Sudan, and a number of Indian troops were infected

In India the distribution is extensive, but the limits of the endemic areas are well defined, the disease being confined to the eastern side of the peninsula Intensely infected isolated villages have been found in the extreme south near Cape Comorin There is a steady incidence of a few hundred cases each year in Madras city The coastal areas are then free up as far as the Ganges delta The whole of the plains of Bengal are heavily infected The endemic area spreads along the Ganges plain into Bihar where the incidence is still high, and to the eastern side of the United Provinces as far as Lucknow, where the incidence gradually tails off, its westerly extension being checked by the dry areas In Bihar it is confined to the Ganges valley, being limited on the north by the Himalayas and on the south by the low laterite hills of the Bihar plateau In a north easterly direction the endemic area extends along the Brahma putra valley into Assam, which province is heavily infected as far as Sibsagar, at present sporadic cases only occur further east From the main Bengal focus the endemic areas extend into eastern Bengal and Sylhet but further extension is pre vented by the high mountain ranges which divide India from Burma It will be interesting to see whether the opening up of direct communications between India and Burma across these mountains will lead to an extension of the disease into Burma on analogy the writer believes that it will not (*see* figure 25)

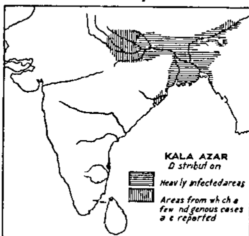
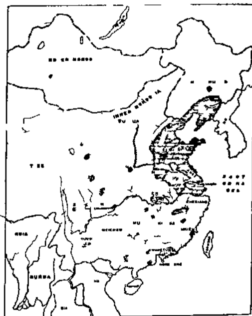


Figure 25 Map showing kala azar distribution in India


Figure 26 Map showing kala azar distribution in China shaded areas

In China the endemic areas are nearly all north of the Yangtse river and are mainly along the line of the grand canal in the provinces of Kiangsu Shantung and Chih-li up to Peiping and further north into Jehol and Fiengtien in Manchuria Cases have also been

There are endemic foci in Transcaucasia and Russian Turkestan It has recently been shown that kala-azar is widespread in the tropical zone in South America and a few cases have been reported from Argentina Isolated cases have been reported from here during the last twenty years, but on the whole the reports were received with scepticism, until light was thrown on the subject by the yellow-fever viscerotomy service in Brazil and Argentina, out of 47,000 viscerotomies, leishmaniæ were found in 41 specimens Subsequent clinical investigations in some of the infected areas brought to light a few cases of kala-azar Nearly all the leishmania-infected viscerotomy specimens and most of the clinical cases came from the north east corner of Brazil between Para and Bahia, but a few kala azar patients were also found in the Chaco district of Argentina The cases were sporadic, and entirely unconnected with one another (*see* figure 27)



Figure 27 Map showing kala-azar distribution in South America

Epidemic features — In most countries in which it exists, kala-azar is sporadic in its occurrence, ... subject to exacerbations of an ... re effective treatment was given, these rises and falls in incidence appear to have had a definite periodicity of about fifteen to twenty years In an endemic area, there was usually a widespread increase in incidence over the whole area, which lasted for three or four years, then there would be a gradual fall, but the disease did not disappear, and even in the trough of the wave the incidence did not drop to less than one-third or a quarter of the incidence at the top of the wave

The character and periodicity of these epidemic waves are probably being disturbed by the extensive treatment campaigns that have been instituted in the most heavily infected provinces, Assam and Bengal, since the beginning of the last epidemic The last epidemic wave started in 1917 and reached its peak about 1923 On previous experience another wave is overdue by at least five years, but provincial health returns give little indication of it, except in the province of Bihar, at the periphery of the endemic area, where no treatment campaign was instituted, and here the increase in the incidence of the disease has recently alarmed the health authorities

In individual villages or in smaller areas within an endemic area, the epidemic wave will be shorter and sharper and may be followed by a period

ease disappears almost completely, but village it may be rising in another not

climatic or other factors or an influenza epidemic,

lied the disease for many lred were attacked within a period of three years, and two years later only one case occurred during the whole year

The disease may also show a true epidemic invasion of an area During the last half-century there have been three epidemic waves in Assam, each has carried the disease further up the Assam valley In the part of the Assam valley adjoining the Bengal plain, kala-azar is now endemic, it appears in epidemic form and between epidemics The disease nd of the valley

Factors determining distribution —In India kala-azar is confined to areas below 2,000 feet, although a few isolated cases of rather doubtful origin have been reported from higher altitudes, and to alluvial soil, to areas with a high humidity, *i e* a mean annual humidity of not less than 70 per cent and with a low mean diurnal range of temperature, *i e* not more than 20°F , it is a disease of rural areas rather than of towns, and when it occurs in the latter it is found in old, low (one storey) and usually damp residences with small compounds in which there is some vegetation and in which fowls, ducks, or goats are kept, *i e* in surroundings very similar to those of the rural areas except that in the towns there are usually organized sanitary services and good water-supplies

Kala azar is a family, house, and site infection, and it was shown in Assam that even burning down a hut and re erecting one on the same site did not check the spread of infection, but that removal of 'coolie lines' a distance of at least three hundred yards was essential

In China also it is a disease of rural areas, but in towns, such as those in the towns in India is reported surroundings with dogs, which are suspected as carriers in some countries, noted

Seasonal incidence —In most of the places where the disease has been studied, a definite seasonal incidence has been noted In Bengal and Assam there is a well-defined peak in the onset curve in the winter months, but it starts to rise in the autumn, the period immediately following the rainy season (*see* figure 28), in Madras the seasonal incidence is less well defined In the Sudan and Abyssinia, *Henderson (1937)* noted that the rise in the seasonal curve started in August which is the height of the rainy season In China the early summer months and in Europe the spring are the periods of highest incidence

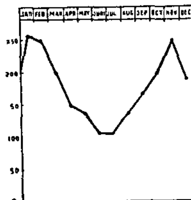


Figure 28 Month of onset of kala azar based on over 2 000 cases seen in Calcutta

Age and sex incidence—In so far as the age incidence of the disease is concerned the endemic areas are sharply divided into two groups In the Mediterranean areas the disease occurs among infants and very young children 93 per cent under the age of five years and is rare among adults On

years This difference in the age incidence has led some workers to regard kala azar in the two regions as being distinct and to use the term 'infantile kala azar' for the disease as it occurs on the Mediterranean littoral The age distribution, however is the only notable point of distinction Even in India kala azar occurs among infants, we reported a case of an infant of less than eight months with well developed kala azar of about four months duration

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Age and sex incidence of kala azar

Age group	Males	Females	Total	Per cent per quinquennial age period
Under 5 years	22	26	48	12.40
5 years but under 10 years	48	57	105	27.13
10 " 15	60	29	89	23.00
15 20	26	20	46	11.88
20 " 30	30	37	67	8.65 × 2
30 40	16	8	24	3.10 × 2
40 " " 50	2	6	8	1.03 × 2
Total	204	183	387	

There is no evidence that either sex is the more susceptible most of the collected figures show a preponderance among males but when the errors of selection are eliminated the difference practically disappears

Race caste and class—There is also no evidence of racial or class immunity In India Europeans and Asiatics are equally liable to infection

when living under comparable conditions The disease is rare among better-class Europeans and Indians living in well-built and well-ventilated houses, but it is very common among poorer-class Europeans and Anglo Indians In some mixed villages the disease seems to predominate among those living in the Mohammedan and Indian Christian quarters the Hindus being comparatively free

ÆTIOLOGY

Causal organism —*Leishmania donovani* is a protozoon of the family Trypanosomidæ, other members of the genus are *L tropica*, the causal organism of cutaneous leishmaniasis or oriental sore, and *L brasiliensis*, the causal organism of South American leishmaniasis, or espundia The parasite of the infantile type of kala-azar has been named *L infantum*, but there is little evidence that this organism differs in any way from *L donovani* The parasite that causes leishmania infection in dogs has been called *L canis*, but there is evidence that, in some instances, at least, this also is identical with *L donovani*

Morphology and Life-cycle of *Leishmania donovani*

Two forms of the parasite are known the non-flagellate or 'round' form, the Leishman-Donovan body, in which form it occurs in the body of its mammalian host and the flagellate form, in which it occurs in its arthropod host (*vide infra*) The development from the round form to the flagellate form will also take place in culture medium

Non-flagellate form —The non-flagellate form is an oval or round body with an average diameter of about 2μ, the breadth in the oval form being about three-quarters of the length It consists of cytoplasm containing a nucleus which is more or less round and a little less than 1μ in diameter, a parabasal body from which springs a rhizoplast, and a vacuole

The Leishman-Donovan body ... and

... In the blood ... which they are ...

... parasites are ... China and in ... the lymphatic glands, but in India it has been difficult to demonstrate them in this site

Viable parasites in this form have been demonstrated in the fæces (Mackie, 1914), in the urine (Shortt, 1923), and in nasal secretion (Forkner and Zia, 1934), their presence in these excreta and secreta must be looked upon as accidental, depending as it does on the separation of small pieces of mucous membrane with its submucosa, which is not the usual result of leishmania infection but is due to some coincident secondary infection

Whilst the immediate viability of these parasites in the stools and nasal secretions has been demonstrated by animal experiment, there is no reason to believe that, outside the body, they remain viable for more than a matter of hours A pure growth of leishmania has been obtained from

sterile urine, but in the presence of other organisms the leishmaniæ are rapidly killed

Flagellate stage—The flagellate form shows several morphological ... generally speaking it is a fusiform organism with a flagel-
... 15μ, the breadth 0 5μ to 2 0μ, and the
... The body of the flagellate consists of
... leus, a parabasal body situated about
midway between the nucleus and the anterior end of the body of the parasite a rhizoplast and flagellum springing from the parabasal body and a vacuole lying between the parabasal body and the anterior end of the body of the parasite (*see* figure 29 and plate B)



Figure 29 Structure of Leishmania in the round and the flagellate or leptomonad stages

N = nucleus V = vacuole
P = parabasal F = flagellum
R = rhizoplast

Culture—A number of different media have been used for the cultivation of leishmania but by far the most satisfactory is NNN or Senekjie s

ie morbid
ion fluid,
30 days)
ion The
at 22°C

its flagellum

It has been shown that in susceptible animals Chinese and Syrian hamsters, *Cricetulus griseus* and *Cricetus auratus*, infection can be caused by the *introduction of either the round or the flagellate forms by the*
p
r
r
m
infra)

Transmission

Historical—Since the discovery of the parasite forty years ago many investigations have been undertaken to discover how kala-azar is transmitted from one person to another Innumerable hypotheses have been propounded and

when living under comparable conditions The disease is rare among better-class Europeans and Indians living in well-built and well-ventilated houses, but it is very common among poorer-class Europeans and Anglo Indians In some mixed villages the disease seems to predominate among those living in the Mohammedan and Indian Christian quarters, the Hindus being comparatively free

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Morphology and Life-cycle of *Leishmania donovani*

Two forms of the parasite are known the non-flagellate or 'round' form, the Leishman-Donovan body, in which form it occurs in the body of its mammalian host and the flagellate form, in which it occurs in its arthropod host (*vide infra*) The development from the round form to the flagellate form will also take place in culture medium

…on-flagellate form is an oval or round … about 2μ, the breadth in the oval form … length It consists of cytoplasm containing a nucleus which is more or less round and a little less than 1μ in diameter, a parabasal body from which springs a rhizoplast, and a vacuole

The Leishman-Donovan body is found in the endothelial cells and large wandering macrophages in all parts of the host's body The parasites are therefore found in the tissues and organs richest in reticulo-endothelial cells, *i e* in the spleen, liver, bone marrow, lymphatic glands and in the submucosa in all parts of the respiratory and intestinal tracts In the blood they are also seen in the polymorphonuclear leucocytes, in which they are

seldom found in the parenchymatous cells of the organs In China and in the Sudan they are said to be found in large numbers in the lymphatic glands, but in India it has been difficult to demonstrate them in this site

Viable parasites in this form have been demonstrated in the fæces … (Forkner … be looked … all pieces … ual result of leishmania infection but is due to some coincident secondary infection

Whilst the immediate viability of these parasites in the stools and nasal secretions has been demonstrated by animal experiment, there is no reason to believe that, outside the body, they remain viable for more than a matter of hours A pure growth of leishmania has been obtained from

sterile urine but in the presence of other organisms the leishmaniæ are rapidly killed

Flagellate stage—The flagellate form shows several morphological h ~ ᵃᵏ ⁿ it is a fusiform organism with a flagel 15μ the breadth 0 5μ to 2 0μ and the The body of the flagellate consists of leus a parabasal body situated about midway between the nucleus and the anterior end of the body of the parasite a rhizoplast and flagellum springing from the parabasal body and a vacuole lying between the parabasal body and the anterior end of the body of the parasite (*see* figure 29 and plate B)



Figure 29 Structure of Leishmania in the round and the flagellate or leptomonad stages

N = nucleus V = vacuole
P = parabasal F = flagellum
R = rhizoplast

Culture—A number of different media have been used for the cultivation of leishmania but by far the most satisfactory is NNN or Senekjie's (*see* p 164) medium The former is a simple saline agar preparation to which about one third fresh rabbit's blood is added while the agar is cooling but is still in the fluid state The blood and agar are then mixed by rotating the tube between the palms and sloped The hydrogen ion concentration need not be adjusted as the blood is an efficient buffer the pH is usually about 7 0 but good growth will take place between pH 4 7 and
l

Survival and pathogenicity—The flagellate form is a very delicate form and contamination with bacteria will rapidly kill a culture The flagellate will not survive in water or soil but survives in sterile milk for a few days When injected subcutaneously it rapidly rounds up and loses its flagellum

It has been shown that in susceptible animals Chinese and Syrian h ~ ~ ~

infra)

Transmission

Historical—Since the discovery of the parasite forty years ago many investigations have been undertaken to discover how kala-azar is transmitted from one person to another Innumerable hypotheses have been propounded and

The finding of parasites in various excreta and secreta has naturally led to the suggestion that direct transmission from man to man might occur in nature, but the epidemiology of the disease negatives these suggestions To take one point only, the strict geographical limitations of the disease seem to indicate some more complicated biological process which demands special meteorological and physiographical conditions This led to the suggestion that leishmania were the natural parasite of some insect and that man was an intermediate host, the bed-bug the flea, and several flying blood-sucking insects were considered and in turn discarded after experimental work had yielded negative results

The workers at the Calcutta School of Tropical Medicine were impressed by the fact that of the various blood sucking insects under suspicion, the local distribution in Calcutta of the sand fly, *Phlebotomus argentipes* corresponded most closely with the distribution of kala-azar and that the geographical distribution of this particular species of sand-fly in India as far as it was known again appeared to correspond with that of kala-azar They showed that under the conditions in which kala-azar was most prevalent, this sand fly was a persistent human-blood feeder and in a series of experiments with laboratory bred *P argentipes* they showed that when these flies were fed on a kala-azar patient, a heavy flagellate infection developed in about 25 per cent of the flies so fed (Knowles Napier, and Smith, 1924), they also found that this same degree of development did not occur in other species Other workers confirmed this observation, and Shortt Barraud, and Craighead (1926) showed that the infection *passed forwards in the sand fly, eventually infecting the buccal cavity*

Later experiments have shown that these sand flies become infected after feeding on persons who have had kala azar and have recovered from the visceral infection but are suffering from that interesting sequel of the infection, post-kala-azar dermal leishmaniasis (*see* p 149), even in cases in which the skin lesions are so ill developed as to be scarcely perceptible (Napier *et al.*, 1933)

Isolated transmissions of the infection to Chinese hamsters *Cricetulus griseus*, by means of the bite of the sand fly were effected (Shortt *et al.*, 1931 and Napier *et al.*, 1933), and the matter was left at this stage for some years More recently, Smith *et al.* (1941) have demonstrated that the survival and progress of the infection in the sand fly depend largely on whether it takes a second blood meal or subsists on fruit or plant juices In the latter case, a large percentage of the infected flies develop a massive infection of leishmania which *blocks the pharynx and buccal cavity* (*vide infra*), *when these 'blocked'* flies are fed on a susceptible animal, infection almost invariably takes place

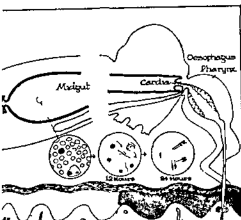
Finally, Swaminath, Shortt and Anderson (1942), by feeding flies according to the technique devised by Smith have transmitted the disease to five out of six human volunteers who were natives of, and lived throughout the period of the experiment in, a non-endemic area

In China the sand-flies associated with kala-azar transmission are *P major* and *P major* var *chinensis*, one or other is prevalent in all the endemic areas of the disease in that country and they have been shown to be efficient carriers (Young and Hertig 1926) In Italy and the Mediterranean area generally both *P major* and *P perniciosus*, especially the latter, are thought to be transmitters, one or other is prevalent in all the endemic areas and Adler and Theodor (1931) have s [illegible] In the Sudan there are thirteen speci [illegible] Lewis, 1940), but a sand fly of th [illegible] *believed to* be the transmitter [illegible]

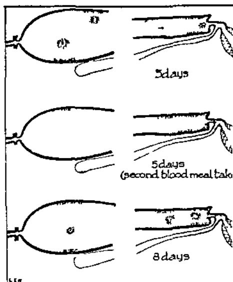
The futu [illegible] or fruit juices on which the sa [illegible] the parasite in the sand flies mo [illegible] future investigation along these li [illegible] remaining anomalies regarding the distribution and incidence of ka [illegible]

The development of the parasite in the sand fly and the mechanism of transmission—The parasite is taken into the mid gut of the sand-fly with its blood meal, *the round form becomes a flagellate form*, and active

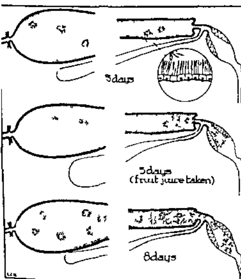
PLATE I (Mechanism of transmission of Kala azar)



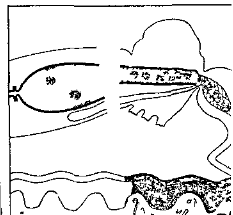
he sandfly takes infected blood into its midgut h s is d gested and leishmania forms are freed evelop into leptomonad forms multiply by binary ission and move forward in the fly s intestinal tract



If the fly takes a second blood meal too earl leptomonad growth is interrupted and a rela light infection results

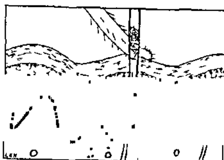


If however it takes fru t or plant juice the leptomonad growth flour shes and the cardia oesophagus and pharynx of the fly become blocked with leptomonad forms

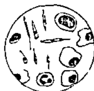


When this blocked fly attempts to feed unable to draw blood past the solid plug of monad forms during its struggle to obtair some of these are detached and are injecte the skin

PLATE II (Pathogenesis of Kala-azar)



Leptomonad forms are injected by a 'blocked' sandfly into the skin





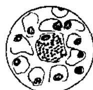
In the skin they immediately lose their flagella and round up. Some are taken up by macrophages others by *polymorphonuclears*



The former multiply, but the latter are digested and disappear



There is a local reaction to the presence of leishmania *in the form of* an aggregation and prolifera tion of tissue and blood



The parasites continue to multiply slowly until *the parasitized cell* bursts

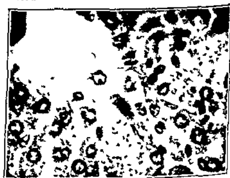


Parasites are then taken up by other macrophages

Eventually *some* of the parasitized cells reach the circulating blood and are carried to the viscera.



In the spleen rapid multiplication occurs and the reticulo-endothelial cells become heavily parasitized. In the figure a parasitized *cell* is seen escaping into the spleen sinus, this will circulate for a time, but will eventually come to rest in some other organ or tissue where if this is rich in *reticulo-endothelial cells further* parasitization and proliferation will take place



In the liver Kupffer's cells are seen heavily parasitized, the parenchyma cells escape infec tion, but appear *to be compressed* by the hy pertrophied Kupffer's cells

division occurs by the third day the infection has reached the cardia by the fifth day the parasites have passed through the œsophageal opening into the pharynx, and by the seventh day the parasites may be found in the buccal cavity If about the fifth day the fly takes another blood meal the flagellate infection is retarded and remains comparatively light if on the other hand it takes fruit or plant juice the infection is not retarded but progresses rapidly to the stage where the œsophagus and pharynx are blocked with a massive flagellate infection

When a blocked fly feeds on man before it can take any blood this solid block of flagellates has to be ejected and it will naturally be injected into the wound made by the sandfly s proboscis There is a little local reaction to this inoculum of flagellates some flagellates will enter the blood stream where they will probably be destroyed but others will be taken up

The sand fly vectors —The three most important species are *Phlebotomus argentipes* Ann & Brun in India *P major* var *chinensis* Newst in China and *P perniciosus* Newst in the Mediterranean area They are all very similar in their habits

Phlebotomus argentipes—This is a dark brown medium-sized sand fly 2.3 to 2.8 mm long on the thorax the dorsum is black and the sides light yellow the wings are rather broader than those of most species and the tarsi are white According to Sinton this species is not found outside India It has a widespread distribution in India but is most prevalent in Bengal and Assam where it can be found at any time of the year but is most prevalent during and immediately after the monsoon (*see* figure 25 plate A)

Phlebotomus major var *chinensis*—The colour is variable dull greyish to bright golden yellow the abdominal hairs are more or less erect dorsally and are a uniform golden grey with very strong silvery lights the disc of the wings has a bluish iridescence the eyes are black and the legs are sometimes darker than the abdomen which is clothed with long recumbent hairs and has tufts of longer upright ones on the dorsal surface This species is closely allied to *P argentipes* from which it is however easily distinguished

l red brown spots lly a similar spot d coxæ are pale es a pale smoky strong light with gest hairs arising are found as in *P papatasii*

Sand fly prevalence —In Bengal there is a small rise in the sand fly [illegible] od between the cool months and the The sand flies are found in the largest from wind currents They are also ouses when these are damp and ill ventilated and have a broken or unpaved floor and especially in rooms with a window opening on to a courtyard where ducks chickens or goats are kept [illegible] ost any hut but they f these walls which n find comparatively

These sand-flies breed in any earth that contains an admixture of nitrogenous matter, the larvæ are found in the corners of broken floors

Bengal obtain their water-supply)

Relation to live stock—They seldom breed far from their food-supply and when the choice is between bovine and human blood they choose the former, on the other hand, they seldom feed on other domestic animals or birds This observation is based on the examination and identification of the blood meals of many sand-flies of this species by the precipitin method (Lloyd and Napier, 1930) The deduction is therefore that cows attract sand-flies to the vicinity but at the same time withdraw the flies' attention from human hosts and are therefore a mixed blessing, on the other hand other animals attract sand-flies by providing a suitable environment for their breeding but do not withdraw their attention and are therefore wholly noxious This fits in with our observations on the distribution of kala azar in towns and mixed villages, the inevitable cow in the Hindu homestead seems to provide some degree of protection to the community

In the laboratory it has been found that these sand-flies must be bred

three months of the year in Bengal and Assam but does not in other provinces, this may account for both the geographical distribution and the seasonal incidence of kala-azar in India

Correlation of sand flies and kala azar—So far as India is concerned every epidemiological observation fits in with the sand fly hypothesis of transmission Further, this sand-fly has actually been found in large numbers in every locality where kala-azar occurs, it is a persistent human blood feeder, a large percentage of the flies that feed on an infected person acquire the infection, infected flies have been found repeatedly in nature, this is not true of other sand-flies, which are more prevalent in the non-endemic areas, nor of insects of any other genus so far experimented with, in this fly an anterior development of the flagellate infection occurs and is unlikely to be purposeless (in *natural flagellate infections which pass* from insect to insect the development is usually posterior), and it has been shown experimentally that the fly is capable of transmitting the infection to man and other mammalian hosts by its bite (*see* p 144) All these facts make it almost certain that this insect is the most important agent in the natural transmission of the disease from man to man in most *localities, although it may not be the only agent*

Sources of infection—It is believed that in India man is the sole naturally, during an attack sent in the peripheral blood, it has been shown that the post-kala-azar dermal lesions will also provide the flagellate infection Further, it has been shown (Napier *et al*, 1933) that a patient treated and cured (of the visceral infection) may still be a source of infection to a sand-fly In such a case the blood culture is negative, so that infection must take place from the parasites that are lying dormant in the skin—the

causes of the later dermal lesions It is thus easy to understand how infection once established in a locality remains endemic

has been reported from Assam

IMMUNOLOGY

Antigenic properties —Noguchi demonstrated that there were differences in the antigenic structure between *L donovani* *L tropica* and *L brasiliensis* but that *L infantum* was antigenically identical with *L donovani* There are strains of *L canis* (of the dog) that are closely related to *L donovani* and others that are related to *L tropica*

It is usually stated that no agglutinins are present in the blood in kala azar but new methods have demonstrated specific agglutinins both flagellar and somatic in infected and immunized experimental animals

The presence of a specific complement fixing antibody was demonstrated by Hindle *et al* (1926) they used a flagellate emulsion as antigen.

Immunity —There is evidence of some natural immunity to infection It has been shown that healthy adult man is not always susceptible

the injection of infected material have have not produced the diseases these volunteers) and two accidental self inoculations by the writer in which no infections occurred and five

are immune to infection with *L canis* There is however no cross immunity against other leishmanial infections *e g* *L tropica* which causes oriental sore

Secondary factors determining infection —Many observations make it seem probable that some secondary factor determines the onset of the disease in a person inoculated with the parasite It has been pointed out that the worst outbreaks in Assam were associated with conditions of

as the malaria epidemic determined the original 1917 which preceded the

On the other hand there is little reason to suppose that general lowering of resistance is an essential preliminary to kala azar infection as weak and debilitated people are not usually picked out, but the writer has suggested that possibly certain specific infections might prepare the way for a general visceral invasion of the parasite in a person in whom it had been lying dormant for some time (the incubation period varies from a few weeks to a year or more) and we have produced epidemiological serological and cytological evidence suggesting that malaria and

enteric were two such infections, part of the evidence for the inclusion of the latter disease was that in Calcutta a large percentage of the patients diagnosed serologically or bacteriologically as enteric fever and coming from parts of the city where kala-azar was endemic subsequently returned to hospital with kala-azar

PATHOLOGY

Morbid anatomy and histopathology—Parasites are found in all parts of the body, particularly *in tissues rich in cells of the reticulo-endotheli* [illegible] he body to invasion appears to be a [illegible] macrophages, the cells of this syst [illegible] iage proliferation actually precedes parasitization, as often the cells in the centre of an island of histiocytic tissue will not be parasitized, whereas those at the periphery are heavily so Nearly all the histological changes observed in the [illegible]

The spleen is almost always enlarged, it may be immense, weighing as much as ten pounds in an adult The capsule is usually thickened and occasionally at the site of recent perisplenitis there is considerable thickening Its consistence is variable, but in most cases it is soft and pulpy, the surface bulging on section of the capsule In the more chronic cases it is firm, retaining its shape on removal from the body but it is usually very friable and is seldom hard and fibrous like the chronic malarial spleen The cut surface has a uniform dark red appearance, if the knife is drawn across the cut surface of the soft type of spleen, quantities of pulp will be scraped off, and the surface will be felt to be quite smooth There may be infarcts

Microscopically, there is infiltration by masses of heavily parasitized macrophages, these encroach on the lymphatic follicles (Malpighian corpuscles), which eventually disappear almost completely There is con siderable enlargement of the vascular spaces The large parasitized macrophages appear to dominate the whole picture

The liver is usually enlarged It is firm, retaining its shape well on removal from the body It is friable, but not so friable as the spleen The capsule is thickened in places and the liver on section shows the greasy appearance associated with fatty degeneration It also shows the nutmeg [illegible] chron call congested liver The cells affected are the [illegible] and parasitized so much that they [illegible] chyma cells, which some writers [illegible] ater stages of the infection The [illegible] d in the portal zone and in some [illegible] othelial cells will be seen in the [illegible] tissue invades the lobules and [illegible] l zone the capillaries are dilated [illegible] he liver cells may be atrophied [illegible] he parenchyma cells Later this [illegible] partially superseded by fibrous tissue producing the interlobular cirrhosis that occurs in the later stages of the disease

[illegible] bone marrow red [illegible] there is a consider [illegible] argely displaced by

proliferating and parasitized macrophages these may occupy almost the whole marrow space but there are usually a few areas of hæmopoietic activity

In other organs and tissues the changes are inconstant and the reports of observers in different countries vary

The changes in the intestinal tract which have been reported from

intestinal tract

The histopathological findings in the skin are somewhat anomalous Workers the skin of a large percent as we in India have failed dermal lesions (*vide infra*) ut is rarely reported in Chi of kala azar too the parasit mall numbers that it is not possible to demonstrate them

Ch the zona fasciculata and zo e commonly but not constan been comparatively rarely

Post kala azar dermal leishmaniasis—When the visceral infection has been overcome either spontaneously or with the aid of treatment some of the parasites in the skin may survive and continue to multiply very slowly taking a year or more to produce clinical lesions In the early hypo pigmented lesion of post kala azar dermal leishmaniasis the ep dermis has undergone very little change but there is some decrease in the pigment in the cells of the basal layer The sub papillary layer is œdematous and the vessels are large and dilated the latter change being very marked in cases with erythematous lesions There is some infiltration by macrophages in the deeper layers around the sub papillary plexus Parasites are scarce in these early lesions but can be demonstrated by cultural met ods and sand flies allowed to feed on these areas become infected As blood cultures are usually negative at this stage the sand flies must obtain the parasites from the local tissues

In the nodular lesions the ep dermis is thinned down to a few layers of cells and the papillæ are flattened out Below in the reticular layer there is much proliferation of the macrophages which form into large masses of cells many of which are parasitized

Blood picture—The most characteristic changes in the blood picture are the leucopenia and the decrease in granulocytes Some degree of anæmia is always present, except possibly in the earliest stages The red

The decrease in leucocytes occurs early in the disease, and is a useful diagnostic sign In 80 per cent of well-developed cases the count is below 4,000 per c mm (*see* figure 30)

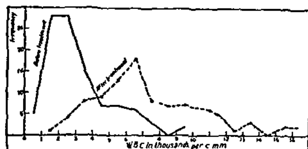


Figure 30 The leucocyte count before and after treatment *frequency curves based on 100 cases*

Agranulocytosis has been described in China, where Zia and Forkner reported seven cases among about 70 cases of kala-azar, but we have rarely seen it in India*

The decrease is almost entirely in the granulocytic elements, which *often drop to 1 000 or even less* Eosinophils are often absent and are usually not more than 1 to 2 per cent of the low total count, this diminution is less noticeable among Europeans in whom the normal eosinophil count is about 2 per cent, but among Indians it is higher, indeed 7 to 10 per cent cannot be considered abnormal among some Indian populations

There is sometimes an absolute increase of large mononuclear cells and there is always a relative increase, it has been shown by supravital staining methods that two-thirds of these cells are histiocytes In the lymphocytes there may be a slight absolute decrease, but there is nearly always a definite relative increase There is usually a marked shift to the left in the Arneth count the mean Arneth index in thirty cases being 92

There is nearly always a reduction in the number of *platelets* the count being usually about 200 000 per c mm

The indirect van den Bergh reaction is nearly always positive, the quantitative test usually shows from 1 to 3 mg of bilirubin per 100 c cm

The *erythrocyte sedimentation rate* (ESR) is very much increased, more consistently so than in any other disease (Napier and Henderson, 1931) The *mean reading* (Westergren) *in 77 mixed cases recently examined was* 68 3 ± 11.2 mm, only in one case was the ESR below 40 mm

—Hydrogen ion concentration of the blood in kala-
the alkaline reserve is reduced The
it that the true change is a reduction

*Though the writer's personal experience of kala azar during the last 20 years amounts to more than ten thousand cases he has only had one case of *complete* agranulocytosis under his charge (Das Gupta and Sen Gupta 1943)

The calcium content is reduced it is usually below 9 milligrammes per 100 c cm The blood sugar is reduced and is sometimes as low as 0 05 per cent The lævulose tolerance is also reduced

and a correspond

on this increase in the euglobulin which is often very considerable in advanced cases

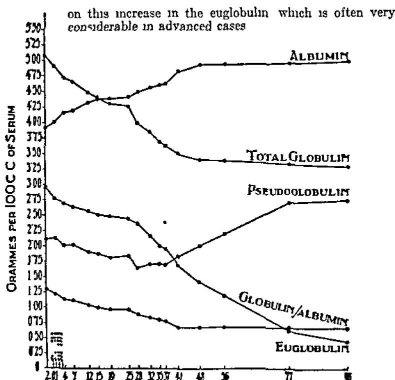


Figure 31 The proportions of the serum proteins before and after treatment the latter is about normal

the moder
imentation
liver dys

Urine —There is nearly always a trace of albumin and marked increase in urobilin Otherwise there is no characteristic change the urine is often concentrated and has the usual characters of a febrile urine during febrile periods

SYMPTOMATOLOGY

Incubation period —There is very little exact information about the incuba
only t
tion p
the wi
eighte

a kala-azar case suggestive symptoms appeared aft
each of
by sand
months
considered to be from two to four months

A case of congenital infection has been reported

Onset—The nature of the onset is not constant, it is sometimes acute, but in many cases it is extremely insidious In India, the cases can be classed, as far as the onset is concerned, into three groups the enteric-like, the malaria-like, and the insidious type

In the **enteric-like type** the patient suffers from general malaise without any localizing symptoms, and the temperature climbs rapidly, reaching 103° or 104°F in about a week, this is maintained for a week or so as a high continuous or a high remittent temperature, and then the temperature gradually falls to 99°F or even to normal Usually abdominal symptoms are absent, the spleen is sometimes just palpable but not tender, the liver is not usually enlarged The attack may simulate one of enteric fevers very closely, but the distinguishing features are a pulse-rate of about 120 a minute and the absence of the typical coated tongue and of the characteristic toxic drowsiness of the enteric patient

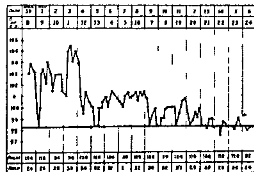


Figure 32 Temperature at onset of kala-azar

The temperature may remain low for a week or so, then it will gradually creep up again In this second febrile attack the temperature is more likely to be remittent or even intermittent, and the classical double rise in the twenty-four hours may appear (*see* figure 33) Meanwhile the spleen will have enlarged and should be definitely palpable by now This attack may be diagnosed as an enteric fever relapse but by the time that a third bout occurs there is little excuse for this mistake

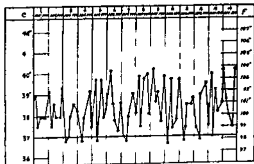


Figure 33 Chart showing double rise of temperature in 24 hours

In the **malaria like type** the onset is sharper, and the fever may be ... to
l
c
s
as it usually does in malaria

In the **insidious type**, the patient cannot give a clear history of the time of onset of the illness but often states that for some months he has not felt well, and possibly he has had attacks of irregular fever Eventually he

comes to hospital because of the size of his spleen or because of some complication such as dysentery or pneumonia and it is obvious from the advanced state of the infection indicated by the serum test that he has been suffering for at least six months

A modification of this is the truly asymptomatic type where the patient s condition is discovered accidentally when for example he happens to bring another patient to hospital

Transient infection —In a few cases with the febrile type of onset the infection has been transient the parasite has been demonstrated by blood culture but meanwhile all the symptoms have subsided and specific treatment has not been given The writer traced a few cases of this kind in which symptoms did not return for three or four years at least the

which treatment was given

Signs and symptoms of the established disease

Unless otherwise stated the following description will apply to a patient

Symptoms — When the disease has reached a comparatively advanced stage the patient complains of fever progressive loss of weight weakness increasing darkening of the skin—usually noticed by his friends—falling of the hair palpitations and dyspnœa intermittent attacks of diarrhœa bleeding from the nose and from the gums and a persistent and very irritating cough Headaches which would be expected with the fever are noticeably absent in most cases and the appetite is good and sometimes ravenous The patient will also usually complain of progressive enlargement of the spleen in some cases this is the first symptom in others the enlargement is not noted for a month or two after the onset of the fever

General appearance —The patient may be emaciated but is often moderately well nourished the hair is dry lustreless and sparse the natural pigmentation of the skin of the forehead of the temples and around the mouth in dark skinned people is intensified and contrasts with the blood

of the second, two inches at the end of the third, and so on, there are, how ever, exceptions to this general rule There is practically no condition i which so rapid an enlargement of the spleen can take place, from being jus palpable a spleen will sometimes reach the level of the umbilicus in a month on the other hand, there are cases in which the enlargement is slow or i checked by the intervention of some inflammatory complication, such a broncho-pneumonia or cancrum oris

The actual size of the spleen is not a very useful diagnostic poin although the regularity and comparative rapidity of the enlargement ma arouse suspicion

The peculiar soft doughy consistence of a kala-azar spleen, howeve is highly significant, it is not common in other conditions, whereas the wood like resistance of an old-standing chronic malarial spleen is uncommon i even a chronic case of kala-azar 'The more chronic the disease the harde the spleen' may be taken as a general rule

[illegible]

[illegible] is probably due to [illegible] colon

Liver — There is nearly always some degree of enlargement of the liver An enlarged soft liver, with a thinned-out edge, overlapping a large sof spleen is very characteristic of the disease Some tenderness is sometime present but is in no way comparable to the tenderness associated with acut hepatitis or liver abscess Occasionally, hepatic enlargement appears to tak the place of splenic enlargement, but usually both conditions are present and there is little evidence that this enlargement is in any way com pensatory, the liver is enlarged in at least 80 per cent of all cases of kala azar, and in those cases in which there is no splenic enlargement the liver is on the whole less often enlarged

Jaundice is not common in the early stages of the disease, but later it may occur and is a bad prognostic sign

[illegible]

words 'continuous', 'remittent', and 'intermittent', and interposing the words 'double' and 'triple' wherever suitable There is, however, one form of fever which, when it occurs, is characteristic of the disease i e the double intermittent or remittent fever, the temperature subsides towards early morning and remains low until about midday, it rises in the after- noon, subsiding again towards evening, about eight or nine o'clock at night it again rises, or the second rise may be delayed until midnight, and again it subsides towards morning In order to demonstrate this double rise it may be necessary to take the temperature every three hours, day and night

PLATE III

Fig 1 A group of kala-azar patients attending a village treatment centre near Cal- cutta Note predominance of children and that some are well nourished

Fig 2 Kala-azar in Indian child typical case

Fig 3 Kala azar in Chinese child with commencing cancrum oris on right side (*Courtesy of Dr E C Faust*)

Fig 1





Fig 3

Bleeding from the gums and epistaxis generally occur Purpuric spot are not very uncommon and are sometimes a terminal symptom in a case running an acute course, they are often associated with uncontrollable hæmorrhage from the gums and into the bowel, a condition suggestive of Henoch's purpura Retinal hæmorrhages have been observed in a few cases

Alimentary tract—Gingivitis, with subsequent loosening of the teeth is common Stomatitis, other than cancrum oris, is not very uncommon at any stage, and in the late stages cancrum oris in the ...
most fatal complica
is not seen so ofte
ment was introduce
far commoner than

The appetite is nearly always good, but the digestion is usually less satisfactory, with the result that intestinal disturbances may result from indiscretions in diet Fractional gastric analyses show that there is little departure from the normal in the gastric acidity

Diarrhœa and dysentery are such common complications that it has been suggested that there is a specific leishmanial dysentery, there is no support for this suggestion Bowel disturbances are comparatively rare in a well-regulated hospital, and respiratory diseases are far more common complications in these circumstances, in the country districts the reverse is usually the case A terminl dysentery sometimes occurs

Respiratory system—The respiratory system is peculiarly prone to inflammatory processes At ...
is usually present without any
account for it In a few cases
disease, seriously interfering wi
suggested that this is due to irritation of the vagus from pressure caused by the enlarged spleen In the later stages, some congestion of the bases of the lungs is common Broncho-pneumonia is a very common complication

The **nervous system** seems peculiarly free from attack by the parasites or their toxins The mental condition is always quite clear, even in the final stages, and delirium is less common during pyrexial attacks in this disease than in any other, a point of diagnostic value

Herpes zoster occurs sometimes during the course of the disease in a patient who is not under treatment but it is much more often seen in a patient receiving antimony injections

Skin and subcutaneous tissues—Certain very prominent changes, probably of a trophic nature, take place in the skin of a kala azar patient

(i) The whole skin surface becomes dry, rough, and harsh The hair falls out and becomes very thin, sometimes children become almost bald

any special liability of the tissues to attack by these organisms Among some peoples in India it is the custom never to allow a patient with fever to have a bath

ase
of
is
the
dryness of the skin It is most evident over the forehead and temples and occasionally around the mouth The blackening is intensified by contrast with the anæmic pallor of the rest of the face This pseudo pigmentation is not seen in Europeans but is very marked in dark skinned Anglo Indians

The skin over the tibiæ is stretched and glossy and this condition is usually associated with pitting over the tibial periosteum

Urinary and reproductive systems — Some symptoms occurring during the course of the disease suggest renal inefficiency *i e* puffiness of the face swelling of the legs and some ascites these are sometimes associated with a decreased output of urine It is probable that the œdema is due to vasomotor disturbances as the urine seldom provides evidence of any serious disturbance of renal function or to disturbance of the albumin globulin ratio

In women amenorrhœa is often an early symptom and is almost invariable in a well established case Although conception is probably

in utero
d Muir
ecropsy

Variations in the clinical picture in different countries

The above description applies to the clinical picture as it is seen in different places in India and it applies generally to the disease as it is seen elsewhere but in some countries the severe form of the disease is more common In the Sudan Stephenson (1940) has described an epidemic in which there was an 84 per cent mortality despite treatment High fever intractable diarrhœa and hæmorrhages are the rule and fatal complications such as cancrum oris and pneumonia are common

Kirk and Sati (1940) have described a punctate rash which usually appears during the course of antimony treatment but sometimes independently of any treatment Similar rashes have from time to time been observed in Indian kala azar but their specificity was questioned They are quite dist
ulcers also ap
(1940) have
by the writer,

SEQUELÆ

Other than post kala azar dermal leishmaniasis there are few sequelæ of importance and there is every reason to believe that after satisfactory treatment most patients recover completely and regain their original state of health A condition of splenomegaly anæmia and leucopenia appears to have occurred about two years after an attack of kala azar in a few of our cases but this syndrome is fairly common in Bengal and the proof that it occurs only in kala azar cases is lacking it has not been reported from elsewhere

clean tongue and the mental alertness of the patient will be helpful signs At this stage the *leucocyte count will usually be about 4,000* per c mm The serum tests will not be very helpful The aldehyde test may be negative, but the experienced will often detect a faint cloud which should

this stage

In the later stages (five months), the points of diagnostic value are the history of a long-continued fever resistant to quinine, progressive enlargement of the spleen, loss of weight, epistaxis or bleeding from the gums, falling of the hair, and increasing darkness of complexion (in dark skinned people) Additional physical signs will be the spongy consistence of the enlarged spleen, the enlargement of the liver, the pulsation of the carotids in the neck, the clean tongue, and the rapid pulse

Leucopenia will now be established, and the *leucocyte count* will almost certainly be below 4,000 and possibly as low as 2,000 per c mm, eosinophils will be few or absent, and granulocytes will form less than 50 per cent in the differential count, and the red cells will number about 3,000,000 and will be slightly hyperchromic The aldehyde test will now be strongly positive If it is desirable to confirm the diagnosis, after failure to find the parasite in the peripheral blood, puncture of the lymphatic glands, sternum, or spleen is the easiest method at this stage

It should be remembered that every sign and symptom of the disease may be absent, the writer has seen many cases that were afebrile for months at a time, if not throughout the disease, and many in which the spleen was not palpable

Therapeutic tests — It may be justifiable to exclude other infections, such as malaria, by giving quinine, but it is never justifiable to give a few antimony injections to exclude kala-azar

If other conditions that require immediate action can be excluded, it is far better to await developments than to rush into a diagnosis of *kala-azar Once treatment is begun, diagnosis becomes far more* difficult Patients do not die in the early stages of the disease (in India, at least) and, although their temperatures may run very high, they do not *suffer much discomfort There is no truth in the oft-repeated statement* that the prognosis is better if the treatment is undertaken early, on the contrary, the best results are obtained in cases in which there is a history of four or ral resistance has ha s treatment *should*

In special circumstances it may be justifiable to make a provisional diagnosis of kala-azar and to give a *full course* of treatment, but once the treatment has been started failure to effect an early improvement must not be allowed to discourage one *Many resistant cases of kala azar give* a history of therapeutic tests and tinkering treatment of this kind

Diagnostic methods

Parasites in peripheral blood present in the depends on the *persistence* searching four films made y Wright

for the opsonic index and stained by Leishman's or Giemsa's method it should be possible to establish a diagnosis in 60 to 70 per cent of cases Casual examination of an ordinary blood smear is of little value

Blood culture should produce a positive result in 100 per cent of cases

agar slope with condensation fluid), these tubes are kept at 22°C and a drop of the condensation fluid is examined at intervals in the fresh state The flagellates will be seen as actively moving forms among the red cells As the medium is easily contaminated it is advisable to sow into at least three tubes

Sternum puncture—Recent experience has shown that this is a very valuable method of diagnosis In a recent series of 80 subsequently proven cases of kala azar parasites were found in the sternum puncture smear in 71, or 89 per cent in six of nine cases in which no parasites were found a

additional method and one that can be employed when the spleen is not puncturable it has not replaced spleen puncture It is a more painful procedure and though probably safer experience has still to prove this

A culture on NNN medium can be made from the material obtained by sternum puncture but it is difficult with the apparatus at present at our disposal to avoid contamination satisfactory cultures will however always show leishmaniæ in a case of kala azar

Technique of sternum puncture—The Salah needle used for sternum puncture is shown below (figure 34) It is made of rustless steel and the bore is about the

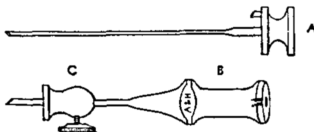


Figure 34 Sternum puncture needle (actual size)

Procedure — The hair over the sternum, if there is any, is first clipped with a pair of scissors, shaved with a razor, and the skin finally cleaned thoroughly with alcohol The best site for the puncture is just to one side of the middle line a *the level of the second intercostal space* This area is first anæsthetized by infiltration with a 2 per-cent solution of novocaine, or its substitute Some solution is first injected into the skin with a fine needle attached to a 2-c cm syringe, then the needle *is pushed down to the periosteum* and the rest of the solution injected About 1 c cm is usually sufficient in a thin individual, but more is required where the subcutaneous tissue is deeper After an interval of 5 to 10 minutes, the actual puncture is made

The apparatus is held with the knob of the stylet in the palm of the hand and the
guard (
are pie
of the
cavity
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sterilize
and the
a dragg
or not Only a few drops of marrow (sinusoidal) blood are removed and the syringe and the sternum-puncture needle are withdrawn, digital pressure is applied over the puncture for a minute or two and the puncture is sealed with collodion With the needle still attached to the syringe one drop is placed into NNN medium and the rest placed on clean slides for smears to be made, these are *stained with Leishman's or Giemsa's stain and examined in the usual way*

Only very rarely will one fail to obtain blood The commonest error is to fail to allow a sufficient length of needle In this case the guard must be adjusted slightly, the stylet replaced and the needle pushed in a little deeper Occasionally the needle goes too deeply and has to be withdrawn slightly before blood will come

Tibia puncture.—This is useful in small children, up to the age of about two years especially as in these young children the sternum is very *soft, and unaided will not usually support the needle while* the stylet is removed The percentage of positive findings is however smaller

The puncture is made about the middle of the shaft of the tibia with a sternum-puncture needle More force is required as the bone is *denser* even than the sternum of an adult

Spleen puncture —The dangers of spleen puncture are *much* exaggerated, but nevertheless it should never be performed unnecessarily or carelessly, and the adoption of a rigid technique is advisable In 95 per cent of cases of kala-azar the parasites will be found in large numbers in the smear (stained by Leishman's or Giemsa's method) and in every case *by cultivation directly into NNN or Senekjie's medium*

Technique of spleen puncture

Preparation of patient —If possible the patient is given a dose of calcium lactate 30 grains on the previous night another dose in the morning and a third dose immediately after the operation The patient is given no food on the morning of the operation, and is kept in bed for the day, he is allowed *food one* hour after the puncture

The writer has followed this procedure whenever possible for over 20 years and he has had no disasters in over 7 000 spleen punctures, he therefore *hesitates* to abandon it, though he is doubtful if it is necessary, or even if the rationale is sound In the out-patient department he has used a considerably modified procedure, reducing *the calcium lactate to two doses and the resting* time to one hour after the puncture, with equally good results

Procedure — The puncture is done with a 5-c cm syringe and a no 11* needle about 1 to 1½ ... attachment should be used ... just

* *No 19 in the*

correspondingly decrease the danger, it is not essential (figure 35) The syringe is oil-sterilized or if an all glass syringe is used it may be dry-sterilized

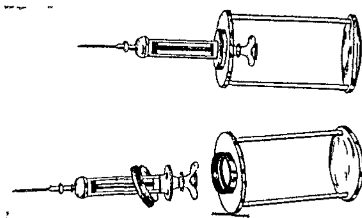


Figure 35 Spleen puncture fitment for syringe

The patient lies on a flat bed with fracture boards if necessary, without a pillow and the operator sits on the edge of the bed on the left of the patient The splenic area is sterilized with alcohol The spot chosen for the puncture is half an inch below the costal margin about the centre of the parietal surface of the spleen at this spot the skin is touched with pure phenol which after a minute is wiped off with a spirit swab If an ordinary syringe is used an assistant standing on the other side of the bed should place his right hand below the spleen to prevent downward movement if the special spleen puncture attachment is used the operator's left hand is free and he can do this himself

The puncture is made in two movements By the first the skin alone is

in the needle and not on any account must the withdrawal of the plunger be continued because blood cannot be seen in the syringe Sometimes the syringe does fill rapidly with blood but this is not a serious matter

A binder should be put round the abdomen with a pad over the point where the puncture was made In about 10 per cent of cases the spleen is tender for the next 24 hours but most patients do not have any discomfort

indicated

In at least 10 per cent of kala azar cases parasites will not be found in the smears although culture will probably give 100 per cent positive results It is usually necessary to make the puncture between the ribs, and also to withdraw the plunger a number of times to be certain of obtaining blood as the organ is not so vascular as the spleen Otherwise there is little difference in the technique

Gland puncture—In China (Cochrane, 1912) and in the Sudan (Kirk and Sati, 1940) gland puncture is found a useful method of diagnosis, in the latter workers' experience, a diagnosis can always be made by this method, but other workers in the Sudan have been less successful In India, we seldom find the lymphatic glands sufficiently enlarged for the puncture to be made, and when, in an emaciated patient, it is possible to grip the glands between the finger and thumb, the findings are usually negative

Procedure—Take a medium-sized dry sterilized hypodermic needle (no 11) Grip a lymphatic gland *e g* an inguinal or a cervical gland between the finger and thumb and after sterilizing the skin plunge the needle into the gland and leave it for half a minute or so Then withdraw it and force out the contained [illegible]

way, scanty leishmaniæ

n It is usually possible

obtain enough fluid with

Culture on laboratory medium—The material obtained by spleen sternum, liver, or gland puncture may be inoculated into NNN or Senekjie's medium This must be done with very strict aseptic precautions

After the spleen puncture has been made the material should first be [illegible]

earlier date Great care must be taken to prevent contamination when a tube is opened A loop of condensation fluid is examined under the high power objective and, if it is positive, rapidly moving leptomonad forms will be seen darting across the field

Senekjie's medium—In 1000 c cm of distilled water dissolve 50 grammes of 'bacto' beef extract Heat at 50° C for one hour and at 80° C for 5 minutes Filter through paper and add —Neopeptone (Difco), 20 grammes, Agar (preferably Nobel), 20 grammes, Sodium chloride, 5 grammes

Adjust to pH 7 2 to 7 4 and autoclave at 15 pounds pressure for 20 minutes

As the agar cools, but before it 'sets', add 10 per cent of defibrinated rabbit's blood Mix by rotating between the palms and slope or pour into a petri dish

Serum tests

The serum tests all depend on the increase in the euglobulin fraction (*vide supra*) *Many modifications have been introduced*, but the writer much prefers the aldehyde test Chopra's antimony test has the advantage of giving a positive result earlier in the disease, but in cases with a large spleen not due to kala-azar it is liable to give a false positive, therefore, in an early case without splenic enlargement, both tests should be done, but in a well established case with a large spleen, the aldehyde test can be relied upon

Aldehyde (Napier) test—This reaction is not fully developed until the third to the fifth month and after successful treatment takes about four months to

test for cure

two drops of commercial formalin are

e serum becomes solid and completely

egg within a very few minutes if it

becomes completely opaque within 24 hours the result is still considered positive Doubtful results are solidification of the serum with various degrees of cloudiness. In a negative result the serum remains crystal clear, although it may solidify

Reading the result—The final result should be read at the end of 24 hours, but with experience a very good idea of the probable result will be obtained in half an hour

(*a*) Positive Solid, white and completely opaque (hard-boiled egg), no light transmitted through the serum If complete opacity is produced in 20 minutes, the result is +++, if in two hours ++, and if in 24 hours, +

(*c*) Doubtful ± Solid, slightly milky but quite transparent after 24 hours

(*d*) Negative (−) Solid but crystal clear after 24 hours

(*e*) Negative —ive Serum unchanged (fluid), after 24 hours

Diagnostic value of test—The test is seldom completely negative after one month from the onset of the disease and after five months it is nearly always

negative diagnosis can be made in a patient with a long history of illness and a spleen b ... uld certainly ... ful result w ... ort history

TABLE II THE INTERPRETATION OF THE RESULTS OF THE ALDEHYDE TEST

Size of spleen / Aldehyde test reading	+++ ++ or +*	(+)	±	(−)	— ive
Below the navel	Kala azar	Doubtful	Not kala-azar	Not kala-azar	Not kala-azar
Four inches or more below costal margin but not below the navel	Kala azar	Probably kala azar*	Possibly kala azar	Probably not kala-azar	Not kala-azar
Two inches or more but less than four below costal margin	Kala azar	Kala azar*	Possibly kala-azar	Probably not kala azar	Doubtful
Palpable but less than two inches below costal margin or not palpable	Kala azar	Kala azar*	Possibly kala azar	Doubtful	Doubtful

*Except when there are obvious signs of advanced tuberculosis or leprosy

Antimony (Chopra) test—The serum is diluted ten times with double distilled water and is placed in a narrow bored test tube, to this, 4 per

Reading the result *Positive* This is indicated by a heavy flocculent precipitate forming almost immediately, this settles as a flocculent mass in the course of half an hour or so

Doubtful This is indicated by a fine granular precipitate which settles more slowly but forms a more compact mass at the bottom of the tube

Negative In a negative result no precipitate occurs

There is usually a doubtful reaction at the end of the first month or even earlier and a positive one at the end of the second or third month In cases of enlarged spleen from other causes, a positive reaction is sometimes given, therefore the test can be relied on only in cases with little splenic enlargement

TABLE III THE INTERPRETATION OF THE RESULTS OF THE ANTIMONY TEST

Size of spleen \ Antimony test reading	Positive	Doubtful	Negative
Below the navel	Doubtful	Not kala-azar	Not kala-azar
Four inches or more below costal margin but not below the navel	Probably kala azar	Doubtful	Not kala azar
Two inches or more but less than four below costal margin	Kala azar *	Doubtful	Probably not kala azar
Palpable but less than two inches below costal margin or not palpable	Kala azar *	Doubtful	Doubtful

* Except when there are obvious signs of advanced tuberculosis or leprosy

The Globulin-precipitation test—In the globulin precipitation test one part of serum is added to three parts of distilled water In kala azar a flocculent precipitate forms The test has the same limitations as the above two tests and is less specific

Other experience—In the Sudan the serum tests have not proved of much value, and in China the more delicate tests which give very misleading results in India *e g* the globulin precipitation test are sometimes preferred to the aldehyde test A recent elaboration is a photometric test with 1 in 1 000 dilution of serum and 1 in 100 urea stibamine solution (d Oelsnitz 1938)

est with a flagellate culture
disease is well established
igen (Grevel Sen Gupta &
nunication) has devised a
ith infected animals

—In the early stages, kala azar has to be diag
specially malaria typhoid fever and
distinctive exanthemata or localiz

(*a*) other febrile diseases especially those in which there are long febrile periods alternating with periods of apyrexia
(*b*) conditions in which the spleen is enlarged
(*c*) conditions in which the liver is enlarged
(*d*) conditions in which there is marked leucopenia

ties ε
fever
the
cirrhosis sch stosomiasis and histoplasmosis In none of these instances will differentiation present any difficulties if the above procedures are followed

Diagnosis of post kala azar dermal leishmaniasis—The hypo pigmented macules and the erythematous rash are clinically very typical and will seldom be mistaken by those with experience of the disease in these cases parasites can be found in the tissues but it is difficult to demonstrate them and there is no simple procedure which can be recom mended for routine use On the other hand in the nodules the parasites can be detected with ease a nodule is seized with a fine pair of forceps
by rubbing
Leishman s
endothelial

PREVENTION

A sufficiently large number of facts regarding the epidemiology of the disease has been accumulated for us to recognize the conditions under which transmission occurs and the first measure of prevention is to avoid these the reader is referred back to pages 139–142

For transmission to occur two factors are necessary (*a*) *the source of infection* and (*b*) *the transmitting insects* and preventive measures can be considered under these two headings

(*a*) **The source of infection**—There are in India as far as we know no animal reservoirs of infection so that man is always the source of infection A patient with kala azar will be the richest source of infection but once treatment has been started the parasites usually disappear from the peripheral blood

The only control measure that has been undertaken on a public health scale has been a treatment campaign Such a scheme was instituted in Assam from the year 1922 on
tion in Bengal a few years lat
had a great influence in co

overdue
which no
d rise in
incidence in the last year or so no similar rise is yet (1942) apparent in the other two provinces

In a small experimental area near Calcutta where we undertook an intensive treatment campaign about 15 years ago there has been no recrudescence of the disease in an area where there were 121 and 137 cases in the years 1925 and 1926 there were no cases in 1937 and only sporadic cases have occurred since

As a case of dermal leishmaniasis is a potential source of danger and as there are always residual cases of this condition in an endemic area it will probably never be possible to eradicate kala azar completely by

means of treatment campaigns, but the disease can apparently be controlled to a great extent, by reducing the sources of infection to a minimum

In the Mediterranean endemic areas and in China, the evidence is accumulating that dogs act as reservoirs of infection An attempt should be made to estimate the extent of the infection amongst the local canine community, and, if it is found to be high, a campaign against all stray dogs should be undertaken

(*b*) The transmitting insects—The conditions under which sand flies (*Phlebotomus argentipes*) flourish have been indicated (p 145)

should be avoided, no dark corners

p

c

paved with cement and no crevices should be allowed, and chloride of

ered earth near the house to destroy the

should be of brick and should be kept

to be preferred and must be kept in

repair In the case of poorer-class dwellings, it is better to have thin *bamboo-matting walls than mud walls or even plastered reeds*

The control of sand-flies in rural areas is very difficult and has yet not become a practicable measure for preventing kala-azar, but the removal of a coolie colony to a new site was practised even before the means of transmission was understood, and the measure proved very successful By

es were left behind and it

es on the new site It was

imply burnt down and re-

the kala-azar epidemic

TREATMENT

Historical—The history of the treatment of kala azar can conveniently be divided into three phases the pre-antimony period the antimony era and the new chemotherapeutic era

The Pre antimony Period—Prior to 1915 kala-azar was, it is said, fatal in 95 per cent of cases ease

disappeared spontai ften

than was previously d of

the *disease* within

The Antimony Era—In 1915 Di Cristina and Caronia introduced the treatment by potassium antimonyl tartrate given intravenously a treatment which had been used two years earlier by Vianna and Machado in American mucocutaneous leishmaniasis This treatment was used in India by Rogers and by Muir later in the same year, later the former introduced a valuable modification using the less toxic sodium antimonyl tartrate

In China and the Sudan on the other hand the result obtained with the antimonyl tartrates was so poor that these drugs were never used systematically

The next important advance was the introduction of the pentavalent antimony compounds *All the earliest and most of the more successful of these have been* prepared by Professor Hans Schmidt Caronia first used sodium *para*-acetyl aminophenyl stibinate clinically in Italy in 1916 After the 1914/18 war when

the prepara this compound

but many writer

in India (paper

1923) and were

successively d the

beginning c ghout

the world urea

stibamine e had

prepared in s used

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Peter

In 1937, Napier Chaudhuri and Rai Chaudhuri first used solustibosan, Bayer 561 a pentavalent compound that can be given intramuscularly and makes a stable solution, so that it can be supplied conveniently in ampoules in our later experience we found it less efficacious than neostibosan

ke used 4 4'-
gland Adler and
, Kirk and Sati
l0) in 8 cases of
r followed this
were antimony-
g was the most

Kirk has also given a short trial to 4 4'-diamidino-diphenoxy pentane and our results so far with this drug have been very satisfactory In some twenty odd cases we have obtained an earlier fall of temperature than with the diamidino-stilbene the fall of blood pressure appears to be less but we cannot yet say whether the neuropathy will follow the injections of this preparation also

Discussion — As far as India was concerned, the introduction of the

h rate among
out the treat
patients were

The advantage of the pentavalent compounds is that they are very much less toxic and can therefore be given in very much larger doses this means that the duration of treatment can be cut down very materially They do not cause some of the serious by effects of the antimonyl tartrates, and consequently the mortality among patients under treatment is very much lower, in our series of more than 500 cases treated by neostibosan, it was only about 2 per cent By an intensive course of treatment the period in hospital can be reduced to one week

per cent more
934, and came
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ewhere in the
e as much
the Sudan
0 per cent,
treatment

was prolonged

The aromatic diamidines appear to constitute another advance, as infinitely better results than hitherto have been obtained in the Sudan, and even in Calcutta our previously more successful results have been surpassed, further, excellent results have been obtained in antimony-resistant cases

Specific treatment

Antimonyl tartrates —The only reason for using the old form of treatment with the antimonyl tartrates is the higher cost of the new preparations Relatively unsatisfactory as the former salts are, they are better than no treatment at all, and in poor countries will probably remain in use for many years

Either the potassium or the sodium salt may be used, but the latter is less toxic A 2 per-cent solution in physiological saline (0 85 per cent in distilled water) is prepared, and to it 0 5 per cent of phenol is added to prevent the growth of moulds This solution will keep for some weeks but it should be examined carefully before it is used to see that there is no precipitate For adults the initial dose is 2 c cm , this should be increased by 1 c cm with each dose up to 5 c cm , the injections must be given intravenously, and if the solution leaks into the tissues very severe reactions will follow, injections should be given on alternate days or three times a week, and, as a minimum twenty-five injections will be necessary

Coughing, vomiting, and joint pains are common accompaniments of this treatment, and it may be necessary to increase the dosage more slowly or even in some cases to reduce it so as to obviate these symptoms, this prolongs the course of treatment and the results are correspondingly less satisfactory

Neostibosan * , di-ethyl amine *para*-amino-phenyl stibinate —This is supplied in sealed ampoules as a light-brown powder, which is dissolved in sterilized distilled water The strength of the solution is not a matter of great importance but we generally use 5 per cent for intravenous injections although strengths up to 25 per cent can be used

In adults it is better to give the drug intravenously, but in children this is often difficult, it can be given intramuscularly, and then a 25 per cent solution should be used, this reduces the bulk of fluid and makes an isotonic solution It should be given into the buttocks on alternate sides there may be slight local reaction but often there is none and abscess formation is very rare Only one abscess occurred in a series of twenty adults treated with intramuscular injections, and we have never seen an abscess in a child

Dosage —The first dose for an adult should be 0 2 and subsequent doses 0 3 gramme The adult dose can be given to children of 60 pounds or more, about 50 pounds 0 25 gramme, about 40 pounds 0 2 gramme, about 30 pounds 0 15 gramme and about 20 pounds 0 1 gramme for the maximum dose may be taken as a rough guide to dosage Children tolerate a relatively larger dose than adults and seem to require it It may be advisable to modify the dosage in very debilitated patients

The injections may be given daily or on alternate days, better results being obtained from daily injections

Length of treatment—It is extremely difficult to be dogmatic about the length of the course of treatment A high rate of cures was obtained by giving eight injections on eight consecutive days Workers in other

* Di ethyl amine *para* amino phenyl stibinate was made by the German I G Farben and marketed under the name neostibosan It is now made by Winthrop and Co and marketed under the same name

countries, especially those in the Sudan, in China and in some of the Mediterranean areas, have not found that this short course is sufficient (*vide supra*). In any case, if the economic aspect does not predominate, it is probably safer to extend the course to twelve injections, but, when it is a matter of curing the largest number of persons with a given quantity of the drug, eight injections constitute probably the optimal course, according to Indian experience.

Response to treatment.—Little notice should be taken of the immediate response of each patient to the treatment, especially when the daily dosage is adopted, as, at the conclusion of a course of treatment, which the subsequent history of the patient shows was successful, the patient may show very little improvement, even the fever remaining until after the last [illegible]

in an average case.

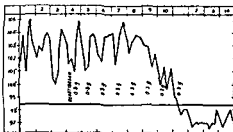


Figure 36. A characteristic response to treatment in an average case.

After three weeks the spleen *should be considerably reduced*, the patient should be gaining weight—he may lose weight for the first two weeks—the leucocyte count should be above 6 000 per c mm, and he should be free from fever. When he is in this state the patient is probably cured, if not, he may be going to relapse, and a second course of injections may be necessary. In some cases however progress is very slow, and unless there is a definite return of fever, which is not due to some complicating infection, it is probably advisable not to embark too readily on a second course but to wait a few weeks before starting it. In the relapsing case the temperature usually mounts slowly, any sharp rise during the course of treatment is generally due to some coincident infection—malaria being by far the commonest in India. In most cases in which malaria supervenes, it is obvious that the disease must have been latent, and when patients come from a malaria endemic area it is advisable to give a course of quinine or other anti-malarial drug as a routine when the antimony course is completed.

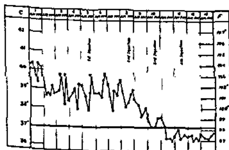


Figure 37. Early response to neostibosan treatment, the temperature remained normal subsequently.

Patients afebrile at the beginning of treatment not uncommonly show a febrile reaction, in the form of a daily rise of temperature or a sharp rise after each injection.

Urea stibamine—Urea stibamine has been extensively used in India and in a series of cases treated in our hospital gave very good results It is slightly more toxic than neostibosan and cannot be given in such large doses, we found that 0·25 gramme was the largest dose that it was advisable to use, but most workers advocate 0·2 gramme as a maximum, the injections should be given on alternate days or three times a week, but not daily The initial dose recommended is 0·05 gramme, the second 0·1 gramme, the third 0·15 gramme, and the fourth and subsequent doses 0·2 gramme The drug

[illegible]

must be used It should be given intravenously If allowed to leak into the subcutaneous tissues or if given intramuscularly, it causes much more pain than neostibosan, but not the very severe reactions caused by sodium antimonyl tartrate The course of treatment is from twelve to fifteen injections

Other antimony preparations—Neostam gave satisfactory results in our cases The dosage is much the same as for neostibosan Antimosan and fouadin are aromatic trivalent compounds, a cure can be effected with either, but they are not so satisfactory as the pentavalent compounds for the visceral form of the disease, about twenty injections being required

Complications associated with antimony treatment—Whereas with the trivalent salts of antimony, coughing, vomiting, joint pains, and the more serious lung complications commonly occur, with the pentavalent compounds, complications are rare With neostibosan practically the only complication that ever occurs is a sharp rise of temperature on the day of the injection this may be accompanied by vomiting Very rarely this is due to some idiosyncrasy on the part of the patient, and the dosage has to be modified until tolerance is established but more often it is due to some defect in the solution We have never traced this to the drug but always to the distilled water in which it is dissolved, since the use of a fresh supply of distilled water has always eliminated the reactions

With some of the pentavalent compounds, but very rarely with neostibosan, a condition suggesting **anaphylactic shock** occurs Usually this does not follow the first injection but one of the later ones, the fifth or sixth, thus suggesting that the patient has been sensitized This reaction has not been observed when daily injections are given, but has been reported in a few cases in which wider spacing of the injections was adopted A few minutes after an injection, the patient's face becomes puffy, and an urticarial rash appears all over the body the voice becomes husky, and the patient has difficulty in breathing he becomes collapsed, and the pulse is imperceptible at the wrist, he often has diarrhœa and vomiting, and he may become cyanosed and unconscious for a few minutes Recovery is usually rapid and is accelerated by an injection of solution of adrenaline hydrochloride and the administration of a diffusible stimulant For the continuance of the treatment, the best course is to employ another compound and to begin with minute doses

With higher doses of urea stibamine and of some of the other compounds, **hæmorrhages** from the gums, nose, and stomach sometimes occur we have also seen retinal hæmorrhages and in one or two cases cerebral hæmorrhages have been suspected

The aromatic diamidines —In our present state of knowledge, great caution should be exercised in using these drugs (*vide supra*) and they should be reserved for antimony resistant cases only The dosage recommended below is that used by the writer who has treated well over a hundred cases with 4 4 diamidino diphenyl ethylene (stilbene) and thirty or so with 4 4 diamidino diphenoxy pentane The immediate reactions described below have been more prominent in the case of the former drug and the late sequel has only been noted with this drug but our experience with the latter has been too short and too recent for us to say that the neuropathological sequel described below does not occur

They are supplied in the form of a white powder in sealed ampoules this is dissolved in distilled water to make a 1 per cent solution and given intravenously The injections are given daily and very slowly The **maximum dose** should not exceed 1 milligramme (0 001 gramme) per pound weight of patient To adults irrespective of size and condition (because we have found that weak emaciated individuals stand the drug best) we give 0 025 g as the initial dose If this is followed by a very severe reaction we give 0 035 g next day but precede the dose by an injection of 0 25 c cm of 1 in 1 000 adrenaline if the reaction is mild we increase the dose to 0 050 g but still give the adrenaline or if there is no reaction we make the next dose 0 050 g without adrenaline The doses are increased as rapidly as possible by 0 010 g or 0 020 g according to the reactions up to
ght of patient to the nearest
whenever there is a marked
possible to omit it after the
maximum has been reached

Children stand the drug better than adults we usually start with 0 010 g and increase the dose by 0 005 g to well over the 0 001 g per pound maximum In a few cases we gave the drug intramuscularly it was distinctly painful and caused a sharp local reaction but produced no abscess The effect seemed to be about as good as when it was given intravenously but we were slightly bolder with our dosage as there was practically no general reaction

We gave 10 injections in the majority of case This meant a varying total dose It is probably safe in our present state of knowledge to aim at a total dose of not less than 0 750 g per 100 pounds weight of patient and 1 000 gramme for resistant cases Other workers have recommended a maximum of 0 001 g per kilogramme but in the writer s experience some of the worst reactions followed the earlier injections which were always small and as he f mum he
considers that it ment or
alternately to risk to have
and greater total doses in his series
obtained cures with total doses varying
grammes in 70 doses and in his later
al dose varied from 0 750 g to 4 900 g

The good effects of treatment with the aromatic diamidines are not immediately apparent and in the vast majority of cases the temperature remains until after the course is complete in fact in many the first few injections appear to cause an exacerbation of all the symptoms The temperature usually falls to normal a day or two after the last injection

about a week later there is a sudden very rapid decrease in the size of the spleen, and the patient then begins to put on weight (*see* figures 38, 39 and 40)

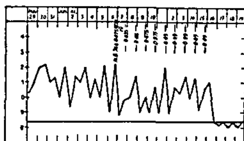


Figure 38 Response to diamidino-stilbene, no fall of temperature until course is complete the usual response

The reactions and sequelæ—Some reactions will be noticed in almost every case The mild reactions include a headache, flushing of the face, sweating and a burning sensation all over the body In the more severe cases the headache will be intense, there will be giddiness, faintness palpitations and epigastric pain and vomiting The most severe symptoms will be collapse, unconsciousness, loss of control of the bowels and urine and loss of conjunctival reflex, in the worst case in the writer's experience, the patient, a well-developed and healthy looking man with no discoverable abnormality except an oriental sore, who had received a dose of less than 0 0005 gramme per pound body weight, remained unconscious for about an hour, but recovered completely in another hour or so

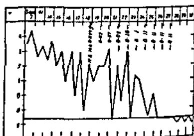


Figure 39 Response to diamidino-stilbene, earlier fall of temperature

As noted above, most of these symptoms can be obviated, or reduced to a minimum by a small dose of adrenaline before the injection of the drug, and a moderate dose after the injection will usually relieve the patient rapidly Where vomiting is prominent, this can be reduced to some extent by giving the drug on an empty stomach, but otherwise it is better to give it not more than two hours after a meal

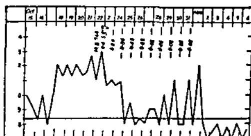


Figure 40 Response to diamidino-stilbene very early fall usually results in a subsequent febrile reaction

In about twenty cases, that is in over half the patients actually seen by us subsequently, a curious neuropathy occurred, namely, a subjective disturbance of sensation over various parts of the trigeminal nerve area hyperæsthesia, paræsthesia, anæsthesia, and formication, and loss of sensation to light touch but preservation of the sense of pressure and pain The first symptom is usually numbness of the area and is noticed about three months after the course is completed The condition has persisted in one case for nearly two years, it showed little increase from the time we first saw the patient, five months after discharge from hospital, and has now decreased slightly (*see* figure 41)

Several patients have been treated with large doses of aneurin without effect, but subjective improvement has appeared to follow the (empirical)

administration of cobra venom, intramuscularly, in doses of 0 1 c cm rising to 1 0 c cm 1 in 100,000, every third day, in a number of cases

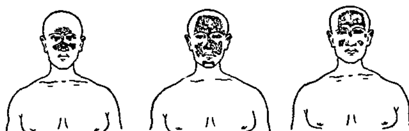


Figure 41 Affected areas in three cases of post-diamidino-stilbene neuropathy

Subsidiary treatment

Very little subsidiary treatment is of any value until the course of specific has been completed indeed, whatever other treatment is given nothing should be allowed to interfere with the course of injections once they have been begun When there are complicating infections such as malaria and hookworm disease the kala azar should be treated first It has been suggested that heavy hookworm infections diminish the effect of the specific kala-azar treatment, there is no evidence that this is the case but treatment of the hookworm infection should always be delayed until one course of antimony has been given, though it is not necessary to wait to see if the cure of the kala-azar is complete

The blood picture will soon return to normal, but this may be accelerated by a course of ferrous sulphate, 9 grains a day for two weeks In cool climates or in the cold weather in India malt and cod liver oil and in the hot weather, compound syrup of hypophosphites, or some other suitable tonic, should be given during convalescence

Diet—As a rule it is not necessary to enforce any severe dietary restrictions unless this is indicated by special symptoms Some patients are always attacked by diarrhœa when allowed a full diet, and when the fever is at its height it is inadvisable to allow a high protein diet, but most patients have a good appetite and do well on a liberal diet Our hospital patients are allowed an ordinary diet unless there is some special contra-indication but for out-patients and others not immediately under control a vegetarian diet with only a little rice plenty of milk and eggs is recommended

Treatment of resistant cases—Other complications should be treated symptomatically A resistant case may be defined as one in which a cure is not effected by an ordinary course of treatment which will cure from 90 to 95 per cent of patients, it is therefore a relative term, but nevertheless

patients seem to be divided fairly sharply into two classes, the ordinary ar the resistant When a patient who has a clear *history of having had* full course of treatment a month or two before is found still to have visceral infection, he should be classed as a resistant case and treate accordingly.

Early experience with
the drugs of choice in resist
or 15 injections in resistant
a mean relative dose of 1 C
cured (apparently) 22 out of 25 antimony-resistant cases

Previously, the course of *neostibosan that we gave in a resistant cas* (adult) was as follows —

Twelve injections in twelve days, beginning with 0 2 followed by 0.3 0 4, and subsequently 0 5 gramme daily, an interval of twelve days, a second series of twelve injections, beginning with a dose of 0 3 gramme another interval of twelve days, and a third series of twelve injection beginning with 0 3 gramme

If the patient shows little sign of improvement during the first serie
of injectio
the seconc
1 part eac
Of this, 1
not occur, a larger dose is injected a day or two later The object is to produce a very severe local reaction The turpentine injections are given coincidently with the antimony injections

In one of the most resistant cases the writer has ever encountered, a cure was effected by the application of the same principle in a slightly more primitive form by a practitioner of the 'indigenous' system of medicine who placed a vesicatory plaster on the patient's abdomen which caused the whole abdominal wall down to the muscle to slough and left a deep ulcer the size of the palm of the hand, when the ulcer healed the kala-azar was cured

When one antimony compound has been used throughout without success, a change to another compound should be tried

Treatment of post kala azar dermal leishmaniasis—Antimony seems to be the only specific for post-kala-azar dermal leishmaniasis, but a cure is not nearly so readily effected as in the visceral form of the disease Preliminary experience with diamidino-stilbene does not suggest that it is of any value in this condition We have generally used one of the pentavalent compounds, but in a few obstinate cases good results have followed the use of the newer trivalent compounds, antimosan and fouadin

The ordinary course of injections, as recommended for the visceral infection, should be given, but the injections should be on alternate days or even more widely spaced One course may be sufficient The nodular lesions will usually show distinct improvement during the first course of *injections, but the hypopigmented lesions usually remain* unchanged gradually regaining their pigment during the course of a month or so Similarly, the shrinking in the nodular lesions will continue for some time after the end of the course of treatment, a period of at least two months should therefore be allowed before it is decided that another course will be necessary.

Injection of a 2-per-cent solution of berberine sulphate into the nodular *lesions* is usually followed by their shrinkage, but this is not a very

practical method when lesions are extensive We have seen a few cases improve on large doses of potassium iodide, given up to the point of producing iodism especially cases in which the nodular lesions were very extensive, the nodules may undergo ulceration, but heal rapidly when the potassium iodide is discontinued.

PROGNOSIS

stage without any symptoms except slight anæmia and great splenomegaly

Death usually occurs from some complicating infection, such as dysentery or pneumonia, or from cancrum oris In infants and young children the disease runs a far more acute course, and the duration is often less than six months

Rarely, in India at least but apparently much more frequently in other countries, especially in the Sudan the disease runs a much more rapid course, after two or three months of high fever purpuric spots appear, there are profuse hæmorrhages from the mucous membranes, and death follows rapidly

From experience in India, the prognosis can be summarized as follows: if no treatment at all is given, 75 per cent of patients will die, the majority within a period of two years In the infantile form the natural duration of the disease is shorter probably about a year If a full course of treatment [illegible]

resid

prom

In a

there were two deaths and five relapses, that is to say an apparent cure rate of 93 per cent

If the disease has lasted more than a year, the patient may be very weak and emaciated and have developed various complications, *e g* cirrhotic changes in the liver Although uncomplicated cases of long

more readily

In Bengal, in about 5 per cent of treated cases post-kala azar dermal leishmaniasis develops This sequel is apparently much rarer, or even unknown, in other localities

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ORIENTAL SORE

Definition —Cutaneous leishm

EPIDEM

Geographical distribution —Or throughout the world than any of t

In Europe several cases have them from the southern portion of cases from Calabria and from sev



Figure 42 Distribution of espundia and American continent and

in
of
are
and well away from the endemic both diseases occur Cases have Souf in the Sahara, the French Africa

In India, the disease is found over the whole of the western and drier portion of the Indo-Gangetic plain; the endemic area extends north into the North-West Frontier Province and Baluchistan and down the west coast of the peninsula as far as Cambay in the Bombay Presidency and east as far as Delhi, further east as far as Benares sporadic cases are reported

In Oceania, instances of oriental sore have been reported from North Queensland

Distribution of oriental sore compared with that of kala-azar—Kala-azar and oriental sore are very rarely present in the same locality, both diseases occur in Crete, and in some parts of Asia Minor they occur side by side and in fact are reported to have appeared simultaneously in the same family In India, oriental sore is found in the dry western half of the Indo-Gangetic plain, whereas kala-azar is confined to the moist [illegible]

[illegible] benign oriental sore might prove a protection against the then deadly kala-azar It has now been satisfactorily shown that cross immunization does not occur

[illegible] easily explained on the grounds of sa[illegible]d-fly of the moist areas being *Phleb*[illegible]nsmitter of kala-azar, whereas *P papatasii* and *P sergenti*, which probably transmit oriental sore, are common sand-flies of the dry areas

Climatic factors—It would be difficult to correlate the various climatic conditions in the endemic areas, and, as they are so widespread, it seems improbable that there are many climatic factors common to these areas Most of the areas of greatest activity, however, lie between latitudes 20° and 45°N These areas have a very hot season, some of them as hot as in any part of the world, and a short cold season in which the night t[illegible] low as zero Most of them are dry are[illegible]ny of them border on desert la[illegible] than on the coast, and the di[illegible]l In India, the disease app[illegible]eas of the western portion of [illegible]

Epidemic features—In the areas where it occurs the disease is usually endemic, but the incidence varies considerably from year to year, and very frequently assumes epidemic proportions [illegible]

[illegible]te, the number of sand-flies decreased [illegible] where the debris provided ideal con-[illegible]ere was an epidemic of oriental sore amongst the troops who helped to clear the area

In Iraq there is a popular association, both with reference to season and locale, between dates and oriental sore, the explanation might well be that sandflies feed on ripe dates (*see* p 145 and Plate V)

Dostrowsky in Palestine reported that family incidence was considerable but this has not been the experience of many other observers and in areas where the disease is sporadic it is by no means uncommon in a family of children for one child alone to be infected

Seasonal incidence —Practically all observers have noted that there is a definite season of onset but this season is not identical in the various endemic areas Dostrowsky reported that in Palestine in most cases the lesions first appeared between the months of September and April *i e* immediately before and during the rainy season Cartron and Bacque said that most of the cases in northern Africa were infected in July August and September Yakimoff and Schockov reported that out of 48 cases seen in Turkestan in January, in one case the sores appeared in June in 7 in July and in 40 in August In Iraq the first cases are usually seen in July the monthly incidence rises up to September or October, after which it begins to fall In the North West Frontier Province and in the Punjab the first cases appear in June and July August and September are the months of the highest incidence A report on oriental sores acquired in Quetta (Goodall) suggested that there the months of maximal infection were September and October The month of infection or if about three months is allowed as an incubation period the first appearance of the lesions usually corresponds with the maximum sand fly incidence

Age race and sex incidence —Persons of all ages and races and of both sexes appear to be equally susceptible In the heavily infected areas children form the bulk of the patients but this is only because the adults have acquired a degree of immunity from having been infected and cured during childhood For the same reason foreigners in endemic areas appear to be particularly susceptible

ÆTIOLOGY

The causal organism —*Leishmania tropica* (Wright 1903) is a protozoon of the family Trypanosomidæ it is indistinguishable morphologically and culturally from *L donovani* the causal organism of kala azar
two parasites
in the round
cells in the gr
ulcer where it
Phlebotomus
passes into its
invasion of th
has not been
rare accident
lymphatic el
along the course of the vessel (*see* plate V figure 5)

In some small animals a generalized blood infection occurs

Transmission —Attention was first focused on the sand-fly as a possible transmitter by Wenyon (1911), who found 6 per cent of the sand-flies in Aleppo, an endemic area, infected with a leptomonad Work on sand flies was continued by the Sergents and others during the next few years, but no very important observation was made In 1919 Acton, by making comparative anatomical 'spot' diagrams of oriental sores and of sand-fly bites and showing the marked similarity between these diagrams, added further support to the sand-fly hypothesis (*see* figures 43 and 44)

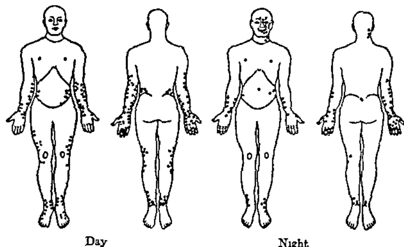


Figure 43 Spot diagram of the position of sand fly bites during the day and night

Sergent, Sergent, Parrot, Donatien and Beguet (1921) produced oriental sore in volunteers in a non endemic area by inoculating crushed sand-

and *P sergen* ,

natural carriers of *L tropica*, and that in special circumstances they were capable of transmitting the infection from host to host In Italy, *P macedonicum* has been incriminated as the transmitter

More recently, Adler and Ber (1941) have actually produced 28 oriental sores in 5 volunteers by the bites of artificially infected sand flies

The mechanism of transmission is believed to be similar to that of kala-azar The sand fly becomes infected by feeding on the indurated

ment of the ... so that, if the fly lives long enough ... ll convey the infection when

a sore can produce the lesion, ... imes occurs, but it is equally certain that it is not the main mode ... smission

Animal reservoirs.—The sporadic incidence of oriental sore has suggested that there is some non human reservoir of infection, and lizards

infected in nature In certain animals, as well as producing local lesions, *Leishmania tropica* causes a generalized infection, so that it is possible that sand-flies may become infected by simply feeding on the blood of infected animals In Turkmenistan, the gerbil, *Rhombomys opimus*, has been found infected in nature, to the extent of 60 per cent of specimens examined Thirty-five per cent of sand-flies living in their burrows have been found infected These animals therefore obviously play an important part in the ætiology of the disease in desert areas

Immunity—Some immunity against subsequent attack is conferred on the patient This is demonstrated in the epidemiology of the disease by the fact that in endemic areas the indigenous adult is comparatively immune, most of the sufferers being children and immigrants Advantage has been taken of this fact, and in certain countries women have inoculated themselves with oriental sore on some covered part of the body as a prophylactic against the disfiguring effect of a sore on the face That this immunity is not complete is shown by the facts that auto-inoculation is not uncommon and that second attacks sometimes occur after the original ulcers have healed completely, of forty-eight cases seen by Yakimoff and Schockov in Turkestan eight had been attacked previously, Marzinowsky and Schourenkoff stated that experimentally produced sores in man only conferred immunity when they ran their natural course, abortive lesions and those subjected to treatment at an early stage failing to produce immunity It is also claimed that there are different strains of *L tropica*, and that immunity is not complete against heterologous strains

There is no reason to suppose that oriental sore confers immunity

PATHOLOGY

The infection is a localized one and there is no general reaction to infection A very definite tissue reaction is caused by the local presence of the parasite, the macrophage apparently playing the main part in this reaction Considerable infiltration of all the layers of the dermis by these cells, many of which contain parasites, extends into the subcutaneous tissues Giant cells are sometimes present The parasites apparently have a special affinity for the endothelial cells of the arterioles and capillaries, which become parasitized and swollen the channels become blocked, and necrosis may follow The cellular proliferation continues and spreads centrifugally, interfering further with the blood supply of the epidermis and reducing it by pressure to a thin membrane which is easily damaged by trauma

Pyogenic organisms eventually find their way through this damaged epidermis, and ulceration occurs The pyogenic organisms invade the

... considerable thickening of the epidermis and occasionally

down growths from the epithelium Leishmaniæ do not invade the epidermis

Eventually the granuloma is invaded and superseded by fibrous tissue and, when the superficial septic process resolves, the epithelium grows in from the edges of the ulcer, a scar, consisting of a thin covering of epithelium over hard fibrous tissue, is left

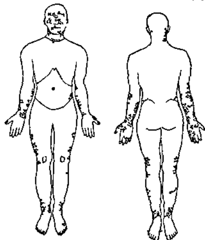


Figure 44 Spot diagram of the sites of sores in Indian troops in Iraq

SYMPTOMATOLOGY

Incubation period —The incubation period is not constant, it may be as short as a fortnight (Marzinowsky and Schourenkoff) or as long as three years (Napier and Halder) Wenyon (1912) inoculated himself, the incubation period was seven months Goodall found that in 57 per cent of his cases the incubation period was at least three months The usual incubation period appears to be from two to six months

Distribution of lesions —The lesions nearly always occur on exposed parts of the body and those in which the epidermis is thin *i e* on the face, ears hands, arms, feet, legs and exposed parts of the trunk. The scalp, the palms of the hands, and soles of the feet are not affected A 'spot' diagram (after Acton) shows the distribution of the sores in Indian troops in Iraq, these soldiers wore 'shorts' and puttees, *i e* their knees were bare (*see* figure 44)

Number of sores —The sores are sometimes single, but more often multiple Occasionally very many sores appear on different parts of the body, figure 4 (plate V) shows a patient with 239 sores

Absence of general symptoms —As a rule general symptoms do not accompany the appearance of the local lesions, but in some cases there is a history of slight fever lasting a few days

The typical sore —A small itching red papule surrounded by a narrow pink halo is first observed at the site of inoculation, this increases in [illegible] scales that vary in colour [illegible] increases in size and [illegible] into a large raised [illegible] usually breaks down under the scab and an ulcer forms the ulcer which is small at first spreads but is usually more or less circular, has clean cut edges a

---

PLATE V

Fig 1—Fungating sore on cheek
Fig 2—Oriental sores on the back of the hands of a British soldier these are beginning to heal
Fig 3—One month later now completely healed repigmentation commencing in left hand
Fig 4—Patient with 239 sores
Fig 5—Ulcerating sore on finger with lymphatic spread nodules appearing along the course of the lymphatics
[Figures 2 and 3 after Goodall (1937) others after Shah (1941)]

Plate V (Oriental sore)



Fig 1

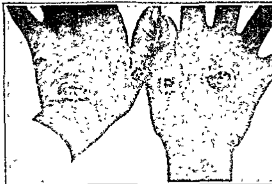


Fig 2

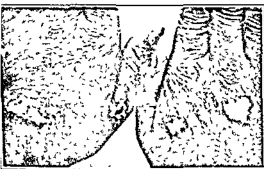


Fig 3



Fig 4



Fig 5



utaneous leishmaniasis in a chicle-gum worker in Yucatan The lesion on ear, one

sloughing and later a granulating base and is surrounded by an area of red induration about a quarter of an inch in breadth The ulcer exudes a sero purulent discharge which may dry and fill the ulcer with a hard dry scab which is difficult to remove If it is left untreated, after a year or so, the sore may heal, leaving a depressed pink or white scar which may cause considerable disfigurement, more especially when contraction of the scar tissue occurs The ulcerating form is always secondarily infected with pyogenic organisms, and in cases of long standing a streptothrix infection which eventually replaces the leishmania is not uncommon

Other clinical types —Other forms of open lesion are the eczematous and the verrucose in the latter form a cauliflower-like growth may involve a large area of the instep for example

There are many non ulcerating forms, the commonest of which is the fleshy nodule that does not break down There are also the keloid and the lupoid forms

The lymph channel [illegible]
draining [illegible]
caused b [illegible]
occasionally found in the lymphatic glands In some cases subcutaneous nodules appear along the line of the lymph channel these eventually break down and become separate ulcers (*see* figure 5 plate V)

The **complications** are those commonly associated with open ulcers Lymphangitis has already been mentioned less often phlebitis and erysipelas occur When the scars contract they leave disfiguring deformities *e g* ectropion

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

After considerable experience with this condition it is easy to make a diagnosis on clinical grounds alone with some degree of certainty, [illegible] actory method [illegible] This is quite [illegible] n ulcers when secondary infection has led to the destruction of the parasites except in the deeper portions of the ulcer After about a year it is seldom possible to demonstrate leishmaniæ, and it is probable that they have died out and that the ulceration is maintained by the secondary organisms

No parasites will be found in the pus taken from the centre of an ulcer, the secondary infecting organism alone being present There are several ways in which the parasites can be demonstrated, if the lesion has not ulcerated or [illegible] 'e method [illegible] h it with [illegible] n so that [illegible] to make a smear from the serous fluid which will subsequently come out Or if this serous fluid is drawn up into a sterile pipette it can be placed into Nicolle Novy and MacNeal (NNN) or Senekjie s medium to obtain a **culture** of the organism

The smear should be examined after staining by Leishman s or by Giemsa s method When any surgical treatment is undertaken a piece of the margin of the ulcer can be removed and a smear made from the cut edge of this piece, or a smear can be made from the deep scrapings of the ulcer after it has been cleaned and washed with saline

Jessner and Amster obtained **specific skin reactions** in dogs and human beings by injection of a dilute blood-free vaccine of flagellates By separating the polysaccharide and protein fractions of the antigen Senekjie believes that he can distinguish between current and past infections

Differential diagnosis —The condition must be differentiated from all other forms of skin nodule, boil and ulcer It is unnecessary to deal fully with all the non-specific boils and ulcers following an injury, or with syphilitic and varicose ulcers of the legs, but a few specific conditions, chiefly tropical or subtropical in their distribution, deserve special mention

Each of these conditions has its characteristic appearance, which is distinct from that of the typical oriental sore, but all of them as well as oriental sore may vary from the typical A knowledge of the geographical distribution of these diseases and of the recent movements of the patient is a most essential preliminary to accurate diagnosis, the final test is the demonstration of the specific organism, which in oriental sores of moderately short duration presents little difficulty

Ulcus tropicum, the sloughing phagedænic ulcer of the tropics, is mainly confined to the legs and occurs in ill-nourished coolies It usually begins with a water-blister or bleb, and sloughing is an earlier and more prominent feature Scrapings from the base of this ulcer, after the slough has been cleaned away, will show the characteristic flora, a spirochæte and a fusiform bacillus

Yaws is a disease of aboriginal races and occurs in all parts of the body, and the lesions are rarely single, the typical lesion is raised above the skin level, and, when the scab is removed, the characteristic 'raspberry' appearance is seen *Treponema pertenue* is found in the lesions, and the Wassermann reaction is positive

Tuberculosis of the skin is not uncommon in the tropics, and, whether in the form of a tuberculide, which is more usual, or of an open ulcer, it may be mistaken for oriental sore, the extreme chronicity of these lesions and the characteristic appearance in the histological sections will settle the diagnosis

The localized, raised and indurated lesions of **leprosy** may be mistaken for the non ulcerating form of oriental sore, microscopical examination will settle the diagnosis Leprotic ulcers will present less difficulty on account of their painlessness In either case other manifestations of leprosy should be looked for but the presence of these does not necessarily exclude oriental sore

Veld sore begins with a vesicle and is usually shallower than the oriental sore, it generally has an undermined edge and is very painful *Corynebacterium diphtheriæ* is easily isolated in the early stages, but chronic sores of the two conditions present considerable difficulty

A primary syphilitic sore on the lip is not at all unlike an oriental sore, nor is a tertiary gummatous ulcer Microscopical examination will settle the diagnosis rapidly in the first case, and in the second a positive Wassermann reaction will be suggestive but not conclusive

PREVENTION

General — The general measures will include the avoidance of the source of infection and of the transmitting sand-fly

All close association with infected human beings and infected dogs should be avoided A dog-destruction campaign should be undertaken where these are suspected as carriers

Sand-flies are very local in their habits, and it is often possible to get out of their range by moving a tent or hut only a few hundred yards the banks of rivers and old brick or mud walls are their favourite habitats, but unfortunately sand-flies will also live in cracks in the ground In special circumstances sand-fly control may be worth attempting (*see* p 320)

Personal —These will include the use of a sand-fly net (45/46 mesh), insect repellents (*see* p 119), and possibly prophylactic inoculation

The production of immunity by the injection of dead vaccine has not yet reached a satisfactory stage Lawrow and Dubowskoj (1937) obtained very satisfactory results by the induction of single sores on the covered parts of the body by the injection of 0 1 to 0.2 c cm of living cultures the sores appear in two to six months, increase in size for a time, and eventually heal in about twelve months' time

TREATMENT

The cure of oriental sore is not so satisfactory as that of the visceral infection, kala azar this is evident from the large number of different forms of treatment that are advocated No satisfactory comparative study has been undertaken since the newer forms of treatment were introduced, and most of the opinions expressed by different workers are based on clinical impressions

The treatment may be (*i*) local or (*ii*) general The local forms of treatment advocated can be considered under the headings (*a*) surgical treatment, (*b*) application of specific drugs, (*c*) physical measures, and (*d*) local injection of specific drugs The general measures consist in the intravenous or intramuscular injection of various antimony preparations

(*i*) *Local* —(*a*) Surgical In the pre-antimony days, surgical measures were mainly relied upon, *e g* vigorous scraping with a Volkmann spoon

adhesive strapping and leaving it without further dressing for a week or more, after thorough scraping and treating with liquefied phenol under an anæsthetic, has given very satisfactory results and is probably the treatment of choice for the more advanced septic ulcers For small ulcers direct application of liquefied phenol without previous scraping is said to be very satisfactory Castor-oil dressings have given satisfactory results in some workers' experiences

(*b*) Application of specific drugs —Those recommended include potassium antimonyl tartrate ointment 2 or even 4 per cent powdered potassium permanganate mercuric chloride mercurous chloride, methylene blue ointment, and powdered sulphonamide, good results have been claimed with each of these drugs by certain workers, but none has proved generally satisfactory

towns this is usually obtainable ready for application in the form of 'dry ice', otherwise a suitable stick can be prepared from a carbon dioxide-gas cylinder The dry ice is applied directly to the sore and held there for at least two minutes by the clock. There is a severe reaction with blistering, but when this has subsided the ulcer usually heals

(*d*) *Local injections* —Emetine hydrochloride has been used very often, 20 minims of a 5 per cent solution are injected into the margins of the sore Mepacrine (atebrin) hydrochloride was suggested some years ago for local infiltration and according to some reports, a few of which are recent, is very satisfactory

The local injection of *berberine sulphate* has in our hands produced some excellent results and is, in the writer's opinion, the best of the drugs used for local infiltration, the drug appears to have a direct specific action on the parasites

If the ulcer is septic, hot magnesium sulphate fomentations and frequent dressings should be used for a few days to make the wound as clean as possible A 2 per cent solution of berberine sulphate is used, this is injected by means of a tuberculin syringe into the indurated area surrounding the ulcer, about six injections will be required for each ulcer in order to infiltrate the whole circumference of the ulcer, but 1 c cm of solution will usually be sufficient for an average sized ulcer There will usually be some inflammatory reaction, which should be allowed to subside before further injections are given, it will usually be possible to give the injections once a week From three to six treatments will effect a cure If there are multiple sores, not more than two or at the most three should be treated at one 'sitting', but treatments can be given daily, the ulcers being taken in turn This treatment however cannot be recommended when there are more than half a dozen ulcers

(*ii*) *General* —The intravenous injection of tartar emetic solution was applied in the treatment of oriental sore immediately after it was introduced for the treatment of kala azar Good results are undoubtedly

writer treated a number of cases with stibosan and later, neostibosan Cures were effected but on the whole the progress was disappointingly slow More recently we have used the aromatic trivalent antimony compounds *e g* fouadin, with rather better results

The dosage for *neostibosan* has already been given under the treatment of kala azar (*see* p 168) It is probably better to give the injections on alternate days rather than daily, and ten to twelve injections will usually be necessary

Fouadin is supplied in ampoules as a 6 3 per cent solution the starting dose is 1 5 c cm and the maximal single dose 5 c cm The injections are given intramuscularly on alternate days or three times a week, and eight to ten injections are usually sufficient

It is too early to be dogmatic but the evidence up to the present suggests that the aromatic diamidines, some of which are so successful in kala azar, are quite useless in this condition

To summarize, in those cases in which there are single or only a few

surgical treatment Until the sore is obviously healing sulphanilamide powder should be included in all dry dressings A judicious combination of surgical treatment with antimony injections will produce the best results in cases with very numerous extensive ulcers

PROGNOSIS

Under normal circumstances there should be no question of mortality from oriental sores, though no doubt many lives have been lost as an *indirect result of these sores, especially when septic complications have* followed The two important points are the time taken in healing and the scarring left behind

The course of an untreated sore is about a year, when eventually it heals it always leaves a disfiguring scar

Under efficient treatment simple sores will often heal in two to three weeks, but the average time taken for septic sores is probably at least two months

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Lesions occur almost always on uncovered parts of the body, on the *ears, face, neck, arms, wrists, legs* and *ankles*, they are usually multiple

The ulcerating type commences as a small red itching papule or as a localized papular erythema The papules go on to pustule formation, break down and form small ulcers The ulcer is surrounded by an œdematous area which event
an ulcer of 9 or 10 cent
usually round, but may be
mined, but later become cle
narrow area of induration There is a purulent exudate In many instances there is lymphatic involvement following on local infiltration around the ulcers, there may be subcutaneous nodule formation along the course of the lymphatics, and the glands become enlarged and painful, this glandular enlargement is not entirely due to septic invasion of the ulcer, since leishmaniæ can be recovered from the glands The glands often fail to regain their natural size after the local condition is cured

The papillomatous type commences in much the same way, but the red papule, instead of becoming a pustule, increases in size and exudes a serous fluid which may form a crust, under this crust, which soon scales off, lies the thin but intact epithelium The non-ulcerating type may eventually, after many months or even years break down and become an ulcer

The mucosal lesions—As already stated, the frequency of the occurrence of the mucosal lesions varies in the different areas of activity of the disease mucosal lesions are rare, but in the le, Klotz and Lindenberg (1923) rep ent of those patients who have had cutaneous lesions for more than two years suffer from mucosal lesions, and Villela, Pestana and Pessoa (1939) that in practically all untreated cases of cutaneous lesion, there is infection of the nasal mucosa which may or may not break down In 12 cases without clinical symptoms referable to the nasal mucosa, 5 showed small lesions, and in the rest, smears made from the mucosa showed leishmaniæ

When they occur, the mucosal lesions usually appear 6 to 18 months after e nasal lesions
has b mmence as an
œdem ollowed by the
form d spread with
the f *ts that 78 per* cent of the lesions are in the nose All the soft pa of the nose, mouth and pharynx may be involved and destroyed The bones and the tongue are not, however, attacked The patient when untreated, usually dies from septic absorption, pneumonia, or starvation from blockage of the passages Costa (1916) described certain ocular complications which have occurred in this condition a new growth in the centre of the cornea, and lesions in the lower eyelid accompanied by opacity of the vitreous

DIAGNOSIS

This does not usually present much difficulty when there are early cutaneous lesions, the indurated edge of the ulcer is pricked and a smear made from the exudate will usually show leishmaniæ (*see* ORIENTAL SORE) In older sores it may be difficult to find them

In cases with mucosal lesions it is usually possible to find the leishmaniæ by scratching the intact part of the mucous membrane of the nose

and making a smear from the exudate Smears from the lesions themselves will seldom show leishmaniæ

The intradermal test of Montenegro is a valuable specific test This is done by injecting intradermally 0 1 c cm of a suspension of a culture of *Leishmania braziliensis* in 0 4 per cent phenol Within 48 hours there is a sharp local reaction which persists up to 72 hours The test first becomes positive after about a month and continues to be positive as long as the lesions remain Complement fixation and agglutination tests have also been used

The condition has to be differentiated from leprosy, frambœsia blastomycosis and syphilis, it differs from the last named in that, in the leishmania infection bones are not attacked and, in syphilis the ulceration does not usually spread beyond the muco cutaneous margin

PREVENTION

The only absolute means of control is by anti sand fly measures, but little is known about the bionomics of sand-flies

The thorough treatment of all cutaneous lesions must be looked upon as the only means of preventing the more serious mucosal lesions that can be applied at present with much hope of success

TREATMENT

This should be both general and local The local treatment recommended for oriental sore (*q v*) can be applied for the cutaneous lesions in this infection but general treatment must also be applied to prevent the later development of mucosal lesions

Vianna and Machado (1913) used potassium antimonyl tartrate by the intravenous route in this disease and thereby initiated a new era in the treatment of leishmaniasis Antimony has been the mainstay in the treatment ever since

The new antimony compounds have been used more recently, and fouadir
most s
of 1 5
on alte

Arsphenamine preparations are sometimes used for the cutaneous lesions, but, whilst curing these (after 3 or 4 injections), they leave the mucous membrane infections intact, nasal ulceration usually follows eventually, and in the end antimony has to be resorted to

Recently it has been claimed that atebrin injected locally and given by mouth at the same time is a specific for the cutaneous lesions, and yatren given intravenously combined with fouadin is said to accelerate the cure of the mucosal lesions

For local application to the mucosal lesions, a bicarbonate of soda gargle for the throat and nose, followed by a wash of 0 1 per cent solution of tartar emetic is said to be useful Another method is spraying with a 2 per cent solution of tartar emetic after anæsthetizing with a spray of 1 per cent cocaine *plus* 1 per cent phenol

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SLEEPING SICKNESS, OR AFRICAN TRYPANOSOMIASIS

Definition—Sleeping sickness is a specific disease confined to tropical Africa, characterized in its early stages by fever, glandular enlargement, and anæmia, and, in its later stages, by progressive involvement of the central nervous system, it is caused by *Trypanosoma gambiense*, or *Trypanosoma rhodesiense*, protozoa of the family Trypanosomidæ, which are transmitted to man by tsetse flies, flies of the genus *Glossina*

Historical—Since the beginning of the 16th century there have been sporadic references to a mysterious lethargy that fell upon the natives of certain parts of equatorial Africa, but with the further development of the slave trade and its penetration into new areas, the commercial implications became apparent, and the casual interest in this disease gave way to a more purposeful one Slaves taken to the West Indies developed the disease shortly after arrival, and, though the disease did not spread there the slave became useless as a slave, and even if he did not die immediately he was a dead loss to the trader. The condition was attributed to homesickness, but nevertheless it was observed that slaves from certain areas were more prone to 'broodin [illegible] slave trade in Africa itself led to [illegible] areas where it spread to the [illegible] the humanitarian and embarras [illegible] reign intruders During the first half of the 19th century, there was a steadily increasing number of references to *la maladie de sommeil* in medical literature, but no material progress in its elucidation was made

[illegible]

the tsetse fly wa [illegible] definite 'fly belt' [illegible] found trypanoson [illegible] that it was the causal organism (In 1880, Evans had demonstrated [illegible] horses in Madras.) He demonstrated [illegible] wild game were [illegible] any disease from the presence of the parasites in their blood

The first recorded finding of a trypanosome in the human blood was that of Nepveu, who, while looking for malaria parasites, found trypanosomes in the blood of a man in Algiers in 1890, but he did not recognize the significance of the observation Forde (1901) was the first to observe

a trypanosome [illegible]
sleeping si[illegible]
This same [illegible]
found the [illegible]
it *Trypano*[illegible]

The first Sleeping Sickness Commission (Royal Society) went out to Uganda in 1902 and Castellani one of its members, discovered trypanosomes in the cerebro spinal fluid of patients suffering from sleeping sickness but was more attracted by some streptococci that he also found The second Royal Society Sleeping Sickness Commission operated from 1903 to 1906 [illegible] commission which proved that sleeping sickness was due to *Trypanosoma gambiense* and that it was transmitted from man to man by the tsetse fly *Glossina palpalis*

Until its ætiology had been thus established sleeping sickness was not recognized as a single syndrome though the natives of Africa themselves and the early clinical observers had noticed that those who had cervical glandular enlargements were liable to the *la maladie de sommeil* at a later date

In 1910, Stephens and Fantham found trypanosomes in the blood of a man who had come from Rhodesia they considered that it differed from *T gambiense* and named it *Trypanosoma rhodesiense* In the following [illegible] was quite distinct and that though similar, they were clinically distinguishable and later it was shown that they responded to treatment very differently

Subsequent investigations have shown that certain other species of *Glossina* are capable of transmitting the infection but only two of these are of any importance namely *G tachinoides*, as a transmitter of *T gambiense* and *G swynnertoni* as a transmitter of *T rhodesiense*

In his work on nagana Bruce visualized only the direct transmission of the infection from animal to animal by the contamination of the [illegible]

For the last thirty years much of the work has been of an epidemio- [illegible] have a common origin and the issue has now tended to become—under what conditions does the trypanosome found in cattle acquire the ability to infect man and conversely—when passaged through bovines under what conditions will the trypanosome causing the Rhodesian type of sleeping sickness lose its properties as a human pathogen? The recent investigations

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Historical—Since the beginning of the 16th century there have been sporadic references to a mysterious lethargy that fell upon the natives of certain parts of equatorial Africa, but with the further development of the slave trade and its penetration into new areas, the commercial implications became apparent, and the casual interest in this disease gave way to a more purposeful one Slaves taken to the West Indies developed the disease shortly after arrival, and, though the disease did not spread there, the slave became useless as a slave, and even if he did not die immediately he was a dead loss to the trader The condition was attributed to homesickness, but nevertheless it was observed that slaves from certain areas were more prone to 'broodi ... rther, the slave trade in Africa itself led to ... into new areas where it spread to the ... disturbed the humanitarian and embarrassed the commercial interests of the foreign intruders During the first half of the 19th century, there was a steadily increasing number of references to *la maladie de sommeil* in medical literature, but no material progress in its elucidation was made

... investigated nagana, in 1895 he ... the blood of cattle dying of this disease and proved ... had demonstrated ... He demonstrated ... at wild game were the reservoirs of infection but did not themselves suffer any disease from the presence of the parasites in their blood

The first recorded finding of a trypanosome in the human blood was that of Nepveu, who, while looking for malaria parasites, found trypanosomes in the blood of a man in Algiers in 1890, but he did not recognize the significance of the observation Forde (1901) was the first to observe

a trypanosome in a case that in retrospect can be recognized clinically as sleeping sickness, but he did not know what the 'worm-like' body was This same patient returned from Gambia to England, and Dutton again found the parasite in his blood, recognized it as a trypanosome, and named it *Trypanosoma gambiense*

The first Sleeping Sickness Commission (Royal Society) went out to *Uganda in 1902, and Castellani, one of its members,* discovered trypanosomes in the cerebrospinal fluid of patients suffering from sleeping sickness, but was more attracted by some streptococci that he also found The second Royal Society Sleeping Sickness Commission operated from 1903 to 1906 with Bruce at its head Not unnaturally Bruce, remembering his

tton in the blood
the whole story,
rried through so
he work of this
to *Trypanosoma*
an by the tsetse
fly, *Glossina palpalis*

Until its ætiology had been thus established, sleeping sickness was not recognized as a single syndrome, though the natives of Africa themselves and the early clinical observers had noticed that those who had cervical glandular enlargements were liable to the *la maladie de sommeil* at a later date

In 1910, Stephens and Fantham found trypanosomes in the blood of a man who had come from Rhodesia, they considered that it differed from *T gambiense* and named it *Trypanosoma rhodesiense* In the following year, Kinghorn and Yorke showed that this trypanosome was transmitted by another tsetse, *Glossina morsitans* It was soon recognized that the geographical distribution of the disease caused by these two trypanosomes was quite distinct and that, though similar, they were clinically distinguishable, and later it was shown that they responded to treatment very differently

Subsequent investigations have shown that certain other species of *Glossina* are capable of transmitting the infection, but only two of these are of any importance, namely *G tachinoides*, as a transmitter of *T gambiense* and *G swynnertoni* as a transmitter of *T rhodesiense*

In his work on nagana, Bruce visualized only the direct transmission of the infection from animal to animal by the contamination of the proboscis of the tsetse, and later, in his work on human trypanosomiasis, he definitely stated that the fly was capable of transmitting the infection only for 48 hours, but later it was shown by numerous workers, led by Kleine (1909), that there was also cyclical transmission that is the trypanosome underwent a cycle of development in the fly before it was transmitted Bruce (1910) at first placed the time interval as five weeks

For the last thirty years much of the work has been of an epidemio-
centred round
e and of which
The problem
at least they
have a common origin, and the issue has now tended to become—under what conditions does the trypanosome found in cattle acquire the ability to infect man, and, conversely—when passaged through bovines, under what conditions will the trypanosome causing the Rhodesian type of sleeping sickness lose its properties as a human pathogen? The recent investigations

of Corson and others between 1930 and 1938 suggest that in both ca the trypanosomes show a considerable degree of stability (Corson, 193

ÆTIOLOGY

The causal organism—As indicated above there are two species trypanosome, *Trypanosoma gambiense* and *Trypanosoma rhodesiense*, th cause the two forms of sleeping sickness, they are protozoa of the cla *Mastigophora, family Trypanosomidæ*

Morphology and staining—These two trypanosomes are morphol gically indistinguishable *in the peripheral blood of man* In the fre specimen of peripheral ' " moving spindl shaped body with an it can be se easily as it disturbs tl irther details its structure the unstained specimen is unsatisfactory

In the blood smear stained by Leishman's or Giemsa's method tl ly 14 to 32 μ in length and 1 ly and a *blepharoplast* at tl passes forward along the who an undulating membrane, an extends for about one-quarter of its length beyond the anterior end of tl body About the middle of the body is an oval shaped nucleus with centrally-placed karyosome (seen only in which occupies about two thirds of the cytoplasm stains a light blue it contair times vacuoles The trophonucleus sta parabasal body and blepharoplast usually appear as one dark-red mas The undulating membrane is a transparent pale-violet membrane

There are two distinct forms of trypanosomes the thin slender form that are the usual ones seen in the peripheral blood and the broad stump ones less frequently encountered in the latter, the flagellum ends with th undulating membrane at the anterior end of the body of the parasite an there is no *free flagellum* *In both types of infection these two form* maintain about the same proportions the slender form always predominat ing, many intermediate forms are recognizable

The parasite multiplies by binary longitudinal division of the trypano some forms, all stages of division may be seen in the peripheral blood

In the cerebrospinal fluid the same forms will be seen, but they ar more pleomorphic, and involution forms are frequently seen

Crithidial forms, in which the blepharoplast is anterior to the nucleus occur at certain stages in the insect vector (*vide infra*), but are not foun in man

Though the two species of trypanosome are identical in the blood o man when the infection is transferred to a laboratory animal, they exhibi certain differences, and in the case of *rhodesiense* infection a percentage often about 5 per cent, of the trypanosomes are 'posterior nuclear' forms, that is the nucleus *is near or actually at the posterior end*, and the blepharoplast is necessarily anterior to it

Culture—Trypanosomes will survive for many weeks in NNN culture medium (*see* p 161), but there is little multiplication, and subcultures canno be obtained

Distribution in the body—Trypanosomes are found in the blood lymph glands and lymph vessels in the early stages of the disease, and in

the later in the cerebrospinal fluid also The parasites never invade the cells but are found in the connective tissue spaces of many organs in the intra cellular spaces of the brain and in the reticular tissue of the spleen and lymph glands.

Pathogenesis in animals—Both trypanosomes will infect laboratory animals rats guinea pigs and rabbits but *rhodesiense* produces a much more virulent infection in these animals further this latter parasite gives rise to the posterior nuclear forms referred to above which are only very rarely found when a *gambiense* infection is transmitted to a laboratory animal

The infection can be transmitted to many species of wild antelope but only one species has been found infected with what appeared to be *T gar*
wo
in
causes nagana (*vide supra et infra*)

In the **tsetse fly,** trypanosomes will be found in the gut mouth parts and salivary glands in all of which sites they multiply (*see* p 202)

Strains—As in many other infections there is evidence that in addition to the differences in species there are a number of different strains of the causal organism which vary in their virulence to man and animals and in their susceptibility to drugs It seems possible that many if not all the puzzling variations in the pathogenicity of trypanosomes in different animal species and in drug resistance might be explainable on a theory of strain selectivity of vectors hosts and drugs

Immunity—There is evidence of both natural and acquired immunity to trypanosome infection

Normally man is resistant to infection with *T brucei* less so to infection with *T rhodesiense* but susceptible to infection with *T gambiense* Yorke and his co workers consider that there is evidence to suggest that in the *presence of special conditions e g some other infection or dietary* deficiencies the trypanocidal action of the blood of man is destroyed and that he then becomes susceptible to infection with *T brucei* which once established acquires a degree of resistance to the trypanocidal action of human blood is capable of establishing itself in a normal individual and becomes what we know as *T rhodesiense* finally as this trypanosome is transmitted rapidly from man to man by the tsetse fly its potentialities for infecting man become still more fixed it loses its pathogenicity for cattle though it still infects them and becomes *T gambiense* There are still many gaps in this attractive theory

On the whole the African native shows a greater degree of immunity than the European intruder in the latter the disease tends to run a more acute course

Transmission—This is effected by the agency of certain species of *Glossina* This may be (*i*) direct or (*ii*) cyclical

Direct—It has been shown that when a fly that is feeding on an infected animal is interrupted and then immediately allowed to feed on another uninfected animal the infection will be transferred to the second animal presumably by the contaminated mouth parts of the fly there is evidence that this occurs in nature and that during epidemic periods in particular infection is transferred from man to man by this means but it is also certain that the cyclical method of transmission is the usual one Certain *Stomoxys* species are capable of transmitting the infection directly

Cyclical—The fly takes the infected bl
(figure 45, 1)
(1*a*) multiply
and broader,
lower free end
this and the ... they continue to multiply for some days, in this extra-peritrophic space they move anteriorly and reach the level of the proventriculus, where they penetrate the peritrophic membrane and reach the lumen of the proventriculus (2*a*) At this stage the trypanosomes are now all long slender forms, they continue to multiply, and still moving forwards they reach the opening of the salivary duct (2*b*) and eventually the salivary glands In the salivary glands they continue to multiply, but undergo a further change of morphology becoming first crithidial (3) and then 'metacyclic (4) forms short forms that are very similar to the short forms seen in the peripheral blood The metacyclic forms are injected with the salivary gland secretion (4*a*) into the wound made by the tsetse fly's proboscis

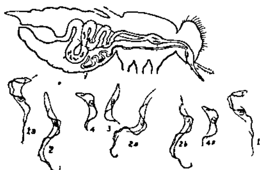


Figure 45 Diagrammatic outline showing position of different forms of trypanosome in the tsetse fly

1 Trypanosome form as found in the peripheral blood in the hypopharynx entering
1*a* Same form in the mid gut
2 Long slender form in the mid gut
2*a* Same form in the proventriculus
2*b* Same form in the hypopharynx on the way to the salivary glands
3 Crithidial form in the salivary glands
4 Metacyclic form in the salivary gland
4*a* Same form in the hypopharynx on the way out

The trypanosome loses its powers of infecting vertebrates soon after it reaches the mid-gut of the fly, but when it reaches the metacyclic stage it again becomes infective, the whole cycle takes from 10 to 25 days according to the circumstances temperature (optimum 75° to 85°F) being the most important factor

In only a proportion of flies—even of the recognized transmitting species—that feed on infected blood do the trypanosomes complete this cycle, but, when once infected, a tsetse fly remains infected indefinitely, the salivary infection being periodically replenished from the extra-peritrophic space Newly hatched flies are more readily infected than older ones that have already taken a number of blood meals

The infection is not transmitted hereditarily in the tsetse

Other possible means of transmission—A few cases of congenital infection have been reported and transmission is also said to occur during coitus

The tsetse fly vectors—There are four species of *Glossina* concerned in the transmission of sleeping sickness, *G palpalis* and *G tachinoides*, *G morsitans* and *G swynnertoni*, in nature the first two transmit the *gambiense* and the latter two the *rhodesiense* infections, though in the laboratory many other species have been shown to be capable of transmitting both infections

Flies of the genus *Glossina* (family Muscidæ) are larger than *Stomoxys*, and have a similar type of proboscis, but a more hairy arista. The characteristic posture of the fly at rest is with wings folded scissor-wise, the wings show distinctive venation. They have a short stout proboscis, thick palpi with broad channels on their inner surfaces in which the proboscis lies (*see* figure 46 and plate I)

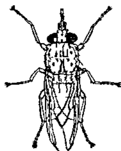


Figure 46 The tsetse fly × 3

compared to a coat sleeve lining that only reaches to the elbow where it ends free the upper end being sewn to the sleeve proper at the shoulder seam



Figure 47 Diagrammatic outline of mid gut of tsetse fly

The female fly does not lay eggs but gives birth periodically (about once a fortnight) to a larva (in girth nearly as big as the female itself) which it drops in a shady spot usually not far from water this larva crawl into a place of safety and immediately pupates. The pupa hatches into an adult after an interval varying from three weeks (at 85°F) to a month or two according to the environmental conditions

Both male and female tsetse flies feed on vertebrate blood and flies of either sex are capable of transmitting trypanosomes. They feed almost exclusively during the day

Reservoirs of infection.—The role of wild game is a controversial subject. As far as the Gambian disease is concerned, it is generally believed that man is the sole source of infection and that game do not play an important part in the ætiology of this infection, many species, of wild game, as well as domestic bovines and pigs, are potential carriers and one species of antelope has been found infected in nature by a trypanosome that appeared to be *T. gambiense*

It is however fairly certain that wild game are [illegible]



Figure 48

infected with the latter trypanosome

EPIDEMIOLOGY

Geographical distribution.—The disease is confined to tropical Africa between 15°N and 20°S

Gambiense infection extends from St Louis in Senegal, north of the Gambia river throughout all the countries on the west coast of Africa down as far as Angola but there are few endemic areas below 10°S It extends as far east as Lake Tanganyika in the south, and further north into Uganda, and to the borders of the Anglo-Egyptian Sudan

Rhodesiense infection has a much more limited distribution, its realm is mainly in the south-east corner of tropical Africa, north, and in few *areas south, of the Zambesi* river, in Mozambique, Nyasaland, Rhodesia and Tanganyika

Figure 49

Epidemic features —The disease is in normal times endemic in the infected areas, but may become epidemic under special circumstances These circumstances have mainly been associated with the opening up of the country and the migration of African natives into infected areas but in other cases the infection has undoubtedly been conveyed into new areas by the personnel of exploratory, commercial, scientific, and religious

much
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Th geria, surveys
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a few surveys have
these s s (Briercliffe,
shown
1940),

The relationship of the disease to wild game has been discussed above

Local distribution—In neither form of the disease is the whole ... ry local ... the big ... in drier ... *imbiense* ... this fact and moved their villages away from rivers and lakes but their need for water for themselves and their animals has necessitated their visiting water ing clearances where they are liable to get infected

Effect of temperature—The geographical distribution indicates that a moderately high temperature is essential and this observation has been supported by laboratory work Kinghorn and Yorke (1912) showed that a temperature between 75° and 85°F was necessary for transmission

Age sex race and occupation—There are little differences in the age and sex susceptibility though men coming in contact with the infecting tsetse fly much more frequently are more liable to become infected however children who look after grazing herds of goats sheep etc during the hottest part of the day naturally rest in the shade and are very liable to be bitten by tsetse flies There is also little evidence of any racial immunity though the inhabitants of the endemic areas suffer a more chronic form of the disease Occupation is a very important factor boat men fishermen and others whose work takes them into closer contact with the tsetse are naturally more frequently infected

PATHOLOGY

Morbid anatomy—When the parasite is injected it causes a local inflammatory reaction which subsides in a week or two the trypanosomes find their way into the blood stream and a septicæmia follows The t

In the lymph glands ... a cellular ... cells in ... ound the ... the size ... rabeculæ ... replaces ... becomes sclerosed

The walls of the blood vessels of the central nervous system the ... the trypan- ... damaged ... tually into ... is there is ... ocytes and

The 'morular' cell is a mulberry-shaped cell specifically associated with this disease, its origin is uncertain, but, as it is usually found in, or in close association with, nervous tissue, it has been suggested that it is a degenerated neuroglia cell, and, as it is also occasionally found elsewhere, it is thought that it may also originate from a plasma cell

There are few changes in the nerve cells, except in the vicinity of the blood vessels, thus the pathological changes in the central nervous system are essentially interstitial and only secondarily parenchymatous

The gross changes in the lymph glands are redness and swelling in the early stages and later ... come hard fibrous masses, ... in the posterior triangle, ... racic, and mesenteric

On opening the skull, the dura-mater may be found adherent, and there will be a generalized lepto-meningitis mainly confined to the vault and the inner surfaces of the hemispheres, there is an excess of cerebro spinal fluid, the brain is usually œdematous and the convolutions are flattened, the ventricles may be dilated, and on section a few areas of softening may be found into which hæmorrhages have taken place

In other organs and tissues, there are few characteristic changes The spleen is usually slightly enlarged, the liver soft and hyperæmic, there is sometimes a subacute nephrosis, myocardial changes have been described and are well developed in experimental trypanosomiasis in monkeys, and the bone marrow is hyperplastic

Cerebrospinal fluid —This will be under normal or slightly raised pressure, 8 to 10 inches of water, and up 30 inches in exceptional cases It is usually clear, and although when there is a high cell count it may be cloudy, definite turbidity suggests some bacterial infection

... cells, an ... There ... ncrease at first, most of the cells being lymphocytes, but the number steadily rises and other cells appear, large mononuclears, plasma cells, morular cells and possibly eosinophils The count may mount to 2,000 per c mm or more, the cell count is apt to be very variable and is not as good a prognostic indicator as is the protein content

Trypanosomes may be present but are not easily found, it will usually be necessary to centrifuge the fluid and examine the deposit They are found in larger numbers in *rhodesiense* infections

... important change is ... the protein content of the fluid This, ... y be 0 1 per cent ... hange not subject ... the parenchyma, whereas a high cell count only suggests inflammation of the meninges

The changes in the cerebrospinal fluid appear very early in some cases, as early as three months from the first onset of clinical symptoms, they usually precede the development of symptoms referable to the central nervous system, and they are present in every case in which these symptoms are well developed

... ent in the peripheral blood They ... *desiense* infection, when they may

Anæmia is common in the later stages of the disease and the red cells have a tendency to clump when blood is taken for a red cell count which fact may make this a very difficult procedure In the differential leucocyte count there is relative increase of large mononuclears

In the **urine** albumin is often found early in the disease and it persists throughout otherwise no specific changes have been reported

SYMPTOMATOLOGY

It is convenient to divide the symptoms of sleeping sickness into two stages [illegible] stage of cerebrospinal involve [illegible] at has survived from the time [illegible] when the two syndromes were [illegible] t be forgotten that the pathological process that produces both these sets of symptoms is a continuous one there are in the first stage many signs and symptoms that suggest meningeal involvement and it is now well recognized that the characteristic changes found in the cerebrospinal fluid precede the development of the typical second stage symptoms by some weeks at least.

Febrile stage—It must also be remembered that there are cases of entirely symptom free infection with *T gambiense* In a survey these symptom free infections may constitute the bulk of the infections identified and whilst a certain number of patients will develop cerebrospinal symptoms at a later date others undoubtedly remain symptom free for years if not for ever This carrier state is more common amongst African natives but Europeans have been found infected during routine blood examination some years after leaving Africa

Between these symptom free and the typical cases there are cases with all degrees of symptom development

The typical case is described below —

The **incubation period** is not well defined it may apparently be as short as seven days though it is usually from two to three weeks before general symptoms appear

The earliest symptom is the local reaction at the site of the bite of the infecting glossina Normally the bite of the tsetse causes local pain followed in those not used to the bite by irritation that subsides in a day or two but in the local inhabitant it will often be unnoticed The infected bite will cause a sharp local reaction that will usually be first noticed within seven days A furuncle appears surrounded by an area of redness and induration this develops into a typical **trypanosomal chancre** a dark red raised button like lesion about an inch in circumference surrounded by an area of erythema and œdema it is very painful on pressure and it lasts two to three weeks This primary lesion has recently attracted much attention as it is realized that it is the rule in European patients though less frequently reported by African natives that it provides an opportunity for early diagnosis as the trypanosomes are easily demonstrated in it and that it thus helps the institution of early treatment

Fever may accompany this primary lesion or follow very shortly after its first appearance There is sudden high fever which reaches 103°F or so within the first 48 hours high fever continues for about a week and then the temperature falls and remains normal or low for a few days before rising again for a few more days After this the temperature

PLATE VIII (Chagas's Disease)



Fig 1—Romaña's sign (after Mazza)



Fig 2—Heart muscle showing *Trypanosoma cruzi* (leishmania forms) (Cour

which may lead to temporary paralyses of groups of muscles, and psychical disturbances mania and delusions, may occur

There is little change in the reflexes until almost the terminal stage, when the knee jerks, after a period of over brisk response, may be absent and the sphincter controls lost The pupils usually react normally

Optic atrophy has been described, even in the absence of any arsenical treatment, and there may be œdema of the disc due to meningeal involvement, with or without increased intracerebral pressure

This stage seldom lasts more than a year if no treatment is given though there have been instances of temporary remission with consequently a much longer duration In more severe cases the end will come within three or four months Death in convulsions has been reported, but the usual termination is from emaciation and complications, *e g* bed sores, bladder *infection*, *pneumonia*, *etc*

DIAGNOSIS

The common clinical signs and symptoms of the early stages are the trypanosome 'chancre', irregular fever, glandular enlargement—particularly in the neck, the rash, and Kerandel's sign, but it will always be advisable to confirm the diagnosis by finding the trypanosome

Certain presumptive laboratory tests will be of value only in cases in which the clinical signs are not characteristic because in a typical case they add little weight to the provisional diagnosis, and parasitological confirmation will still be necessary

To carry out a survey in an endemic area after a preliminary selection of suspected cases by gland palpation thick film examination, gland puncture and lumbar puncture should be done

In the later stages, the parasites in the blood are very scanty and the glands may be sclerosed In these cases the cerebrospinal fluid will be the only medium of diagnosis, even in the absence of trypanosomes, which are always difficult to find characteristic changes in this fluid are considered to be diagnostic

The confirmatory and presumptive methods of diagnosis can be summarized as follows :—

Confirmatory methods.—(i) Direct examination of fluid from the primary lesion (trypanosome chancre).

(ii) Gland puncture

(iii) Examination of the peripheral blood, (a) direct coverslip examination, (b) by the thick-film method, and (c) after triple centrifugalization.

(iv) Lumbar puncture.

(v) Animal inoculation

Technique.—(i) The indurated margin of the lesion is pricked with a needle and the fluid that exudes is examined under a coverslip, or a smear is made, stained by *Giemsa's method, and examined*

(ii) The skin over the gland to be punctured is sterilized, and the gland is held firmly with the left hand while a hypodermic needle of wide bore is thrust

e

e

(iii) (a) A drop of blood taken from the finger or ear-lobe is mixed with an equal quantity of citrate saline and examined under a vaseline-ringed coverslip with a 1/6 inch objective, the attention will be drawn to the trypanosome by the movement of the red cells

(b) the thick-film methods of examining for malaria parasites (*see* p 87) can be utilized, Field's rapid-staining method gives excellent results

(c) About 5 c cm of blood is withdrawn, placed in a centrifuge tube containing 1 c cm of 2 per cent sodium citrate solution, and centrifuged at low speed

will throw down the majority

and centrifuged again at the

the leucocytes are deposited

ged a third time at a rapid

now examined, directly under

can be obtained by either lumbar or cisternal

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ngthen

the evidence

Pandy's test is a simple and most useful test to carry out in the field One

of carbolic acid solution (1 part

to cloud

nervous system

(v) Of laboratory animals, mice, rats, guinea-pigs and rabbits are all susceptible to infection, and strains can be maintained for long periods by passage through these animals, but to establish a strain in the laboratory, it is usually necessary to make the first passage through a monkey, *Silenus rhesus* or some

The deposit of 5 c cm of citrated triple-centrifugalized

key, subsequent passages

ording to the *size of the*

used in the same way

A differential diagnosis between *T. gambiense* and *T. rhodesiense* can be satisfactorily made only by animal inoculation; in the latter, the

infection is much more virulent, and posterior-nuclear forms will appear (*vide supra*).

[illegible] when blood [illegible] y constantly [illegible] y be noticed [illegible] d should at once arouse suspicion, so that the gland juice can be examined for a longer period than usual before being pronounced negative

(ii) Brown's adhesion phenomenon depends on the fact that, in the presence of immune serum, platelets and other small particles (*e g* bacilli) will adhere to trypanosomes, it is claimed that the test is species-specific.

(iii) The serum-formalin test is carried out in the same way as for kala-azar (see p 164)

The 'positive' result is not as clear-cut as in kala-azar, though a definite change occurs in all advanced cases of sleeping sickness, and many other conditions produce confusing results, so that it is not a test of great value in the human disease, as it is in animal trypanosomiasis, *e g* camel trypanosomiasis in which it is the routine diagnostic procedure

TREATMENT

Historical.—From the earliest days, arsenic in one form or another has been [illegible] in 1910

In 1908 Plimmer and Thomson showed that intravenous sodium antimonyl tartrate caused trypanosomes to disappear from the blood of experimental animals, Kerandel claimed to have cured himself with potassium antimonyl tartrate after atoxyl had failed

Many other arsenical antimonyl preparations were introduced and tried but [illegible] propane are believed from more limited experience to be superior It was again at the Liverpool School of Tropical Medicine by Yorke (1940) and his co-workers that this group of drugs was introduced

An 'incident' in the history of the treatment of sleeping sickness was the wide publicity given in the early inter-war period to the now finally discarded salvarsanized serum treatment

[illegible]

Specific drugs and dosages —At the present day, the only specific drugs that have survived an extensive trial are—atoxyl, which is now

practically obsolete, orsanine, and germanin (or antrypol, a British product which is *identical with germanin**), for treatment in the first stage and tryparsamide for the meningo-encephalitic stage, orsanine is also used in the latter stage but its value is very limited The antimonials may be looked upon as an adjuvant treatment in arsenic-resistant cases The aromatic diamidines show considerable promise, but have not yet undergone the test of time

Atoxyl is given in a 10 per cent solution in sterile distilled water, in doses [illegible] *weight, weekly for six* to ten [illegible] tes can be expected, but toxic [illegible]

[illegible] tramuscularly, or intravenously in [illegible] water, in doses of 20 to 35 mg [illegible] imum individual dose is usually [illegible] tions are given weekly for ten to twelve weeks It is less toxic and more efficient than atoxyl in sterilizing the peripheral blood in the early stages, but it is far less efficient than tryparsamide in the meningo encephalitic stage, though it is still used in this stage.

Tryparsamide is given intravenously in a 20 to 40 per cent solution in sterile distilled water, in doses *of 20 to 40 mg per kilogramme body-weight,* up to a maximum individual dose of 3 grammes in an adult, at weekly intervals for 10 weeks Chesterman recommends larger doses, of the order of 60 mg per kilogramme in adults, with a maximum of 4 grammes for an individual dose This drug has a relatively poor trypanocidal action and is therefore not given in the early stages, but it appears to possess special powers of penetrating nervous tissues, and is therefore the drug of choice in the late stages of the disease

Antrypol or **germanin** is given intravenously in a 10 per cent solution in sterile normal saline, in doses of a gramme for an adult twice or thrice *weekly, up to a total dose of 10 grammes*

4 4'-diamidino diphenyl ethylene diphenoxy pentane, and diphenoxy *propane,* the members of the diamidine group that have so far been used are given in a 2 per cent solution in sterile distilled water, in doses of 1 mg. per kilogramme body-weight thrice weekly, up to 15 injections

Antimony preparations—Sodium antimonyl tartrate has been largely superseded by other less toxic drugs The trivalent fouadin and the pentavalent *neostibosan have been used with some success and are given* in the dosages used in leishmaniasis (*see* p 168)

Toxic effects—*All the pentavalent arsenical drugs may give rise to* toxic symptoms even when given in moderate doses, but the likelihood of this occurring increases with the dose Each drug has its own specific range of toxicity, and individual susceptibility is a variable *factor*

Occasionally, severe diarrhœa and vomiting will occur, liver disturbances and dermatitis are rarer *than with the trivalent arsenicals, but do* occur Visual disturbances are usually the limiting factor, these may be serious The earliest symptoms are dimness of vision, contraction of the visual field and sometimes flickerings Later, blind spots will appear and eventually there will be complete blindness

* A French product moranyl (Fourneau 309) is also identical with germanin

Little change will be seen by use of the ophthalmoscope until permanent and irreparable damage is done Therefore a patient having tryparsamide should if practicable have his vision tested before the course is started, and then before *each* subsequent dose, if there is any deterioration of vision the tryparsamide should be stopped immediately If this is done directly the early symptoms appear, the vision will usually improve again

Optic atrophy is more likely to occur in advanced second-stage cases than in early cases, and is due both to the disease—which alone will occasionally produce it—and to the treatment

When one is treating uneducated African natives it will be impossible to test their vision accurately and one has to face the fact that in a certain proportion of cases blindness will occur and to hope that if treatment is stopped immediately they will recover

[illegible]

Certain alarming, both early and late, toxic effects from 4 4′-diamidino diphenyl ethylene have recently been reported

The treatment of the case—Early institution of treatment is very important as the trypanosome is very much more easily killed before it has established itself in the meninges and brain The *gambiense* infection is much more amenable to treatment than the *rhodesiense*, which is very apt to become arsenic-fast

In the first stage of either infection, antrypol is the drug of choice, but in *gambiense* infection orsanine may be used as an alternative Yorke considers that the danger of making a *rhodesiense* case arsenic-resistant should deter one from using any arsenic drug in the early stages

[illegible]

In the meningo encephalitic stage, tryparsamide is the only really satisfactory drug Orsanine will undoubtedly produce cures in this stage, and claims as high as 50 per cent have been made for it, but it is generally agreed that it is inferior to tryparsamide

[illegible] physician must resort to antimony pre- [illegible] courses, and to antrypol, though the [illegible] when once changes have occurred in [illegible]

The art of the treatment of this disease resolves itself into striking a balance between the toxic and the efficient dose of the trypanocidal drugs, and playing them in such a way that the infection does not become drug-resistant—this drug resistance is not confined to the arsenic compounds Inadequate dosage certainly tends to produce drug-resistance Chesterman

takes the view that in the treatment of an otherwise fatal disease one should be prepared to risk the complications that larger doses may cause Obviously this is a matter of circumstances as well as opinion

General and subsidiary treatment—The circumstances are not usually such that the patient can be confined to bed, but when this is possible it should certainly be done, at least during the febrile stage In both this and the later stages, good nursing is of the greatest importance, in the latter in particular, bed-sores, hypostatic pneumonia, etc, are very likely to occur unless great care is taken

Concomitant infection, such as hookworm, malaria, etc, must first be treated to allow the specific drugs to exert their full action

Drug-resistance—This is an interesting phenomenon, the full explanation of which has not yet been given Drug-resistance may be a function of the parasite, or of the host It is easier to conceive of it as a function of the latter, but it is believed in this case to be one of the former

After treatment by the pentavalent arsenic compounds, it is sometimes found that the infection from which the patient is suffering is arsenic-resistant, that is to say, further treatment by any of the pentavalent arsenic compounds, and to a less extent the pentavalent antimony compounds, will not affect the try
mitted to another man,
character, in fact, no
the insect vectors will alter the arsenic-resistant character of the strain

Antrypol-resistant strains have also been isolated, but not so readily

Drug-resistant strains are more frequently encountered in *T rhodesiense* than in *T gambiense* infections, but they have been found in the latter, in areas where wholesale inadequate treatment has been undertaken

The theory that appeals to the writer is as follows . In man (and
-osome with slightly
on, when a number
predominates but the
their stronger rivals
are knocked out (*cf* malaria) Eventually, all drug-susceptible strains *are knocked out*, drug-resistant strains are thus *selected*, and not *made* If this theory is established, some revision of the principles of treatment will be necessary

PREVENTION

Before considering preventive measures it will be as well to review the essential factors in transmission, these are (*i*) the trypanosome and its 'reservoirs', (*ii*) the tsetse fly, (*iii*) susceptible man, and (*iv*) contact between the tsetse and man

Preventive measures must be considered in connection with each of the factors —

(*i*) The ... and its 'reservoirs'—In *gambiense* infection
man is the m ... ve been made to
reduce this re ... mpaigns, in which
very large nu ... rate only a few,

injections of some arsenical compound e g orsanine Cure is not effected but temporary sterilization or at any rate a marked reduction in the

possible wild game reservoir of *rhodesiense* infection opens up controversial subjects which it would be out of place to raise here

(ii) The tsetse fly —*G palpalis* remains near the shores of lakes and

of bush (Symes and Southby 1938) Trapping and other special methods have been introduced in special circumstances

apparent success

Rules have from time to time been put into operation to prevent migration of susceptible natives into infected areas but are difficult to enforce

(iv) Contact between the tsetse and man —As the tsetse bites during the day it is difficult to devise means of protection Clothing certainly helps to protect the European sojourner Night travel has in the past been resorted to in order to avoid infection

The location of settlements away from rivers and lakes and the aggregation of the population into relatively large villages as opposed to wide distribution in scattered homesteads are measures that are now being adopted It is possible to make wide clearings around these villages and of course this should be extended to the roads as far as possible

Gibbins (1941) has recently investigated the use of rod shaped clearings along streams watering places and road crossings These clearings discourage *G palpalis* from lingering to bite man

As in the case of almost every tropical disease the economic agricultural and nutritional aspects of control loom large and the subject has to be studied from all these points of view

PROGNOSIS

Untreated *gambiense* infection may run a very chronic course of some years duration whereas *rhodesiense* infection usually runs a rapid course of a few months duration but there are exceptions in each instance

Prognosis in the treated case will depend on the stage at which the diagnosis is made and treatment instituted on the species of infecting

the prognosis is usually much graver

To this general rule there are exceptions, some strains of *T gambiense* are very resistant to treatment, and there are strains of *T rhodesiense* that respond readily

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CHAGAS'S DISEASE, OR SOUTH AMERICAN TRYPANOSOMIASIS

Definition—South American trypanosomiasis or Chagas's disease is usually acute in its early stages and is characterized by local swellings fever adenitis and anæmia and later develops varied chronic manifestations cardiac nervous or myxœdematous it mainly affects children and it occurs in South and Central America It is caused by *Trypanosoma cruzi* which is transmitted to man by reduviid bugs of the family Triatomidæ notably *Triatoma megista* and *Triatoma infestans*

Historical.—The history of this disease is almost unique in that the causal organism and the mode of transmission were discovered in the laboratory before

(Packchanian 1940)

ÆTIOLOGY

The causal organism —This is now classed as a trypanosome, but in view of certain differences between it and other trypanosomes, it was at one time placed in a separate genus, *Schizotrypanum*

Morphology and staining —It has two forms, a flagellate form in the transmitting insect and in the blood of the vertebrate host, and a leishmania form in the solid tissues of the latter The flagellate form passes through various developmental stages, appearing as a trypanosome, a crithidia, and a leptomonas in the insect vector, and also probably in the vertebrate hosts' tissues

In the blood, only trypanosome forms are seen, these may be either short stumpy or long slender forms In their morphology and staining, they differ very little from the trypanosomes of the African disease (*q v*), but they are slightly larger, measuring about 20μ as a rule The stained specimen assumes a characteristic C shape (*see* plate B)

When they invade the host cells, they lose their undulating membrane and flagellum, and become leishmania forms (*see* KALA-AZAR), 1 5 to 4 μ in diameter They multiply rapidly by binary fission and destroy the host cell which eventually brusts, when they may find their way into other cells, or back into the lymphatic fluid and blood, but it is only trypanosome forms that are seen in the latter

Distribution in the human host —As noted above, the trypanosome forms are found in the blood, though in the human host they are very scanty in the peripheral blood The leishmania forms are found mainly in the endothelial cells of the capillaries and lymphatics, and in the heart muscle, but they also invade the cells of the skeletal muscles They thus occur in nearly all the organs and tissues of the body, spleen, liver, suprarenals, ovaries, testes, thyroid, brain, bone marrow, mucous membranes, and subcutaneous tissue They have also been found in the cells of the epidermis

Transmission —There are many potential vectors but, as far as is known at the present time, two species are mainly responsible for the transmission of the disease to man, namely *Triatoma megista* and *Triatoma infestans* In the endemic areas these bugs are repeatedly found infected in nature, sometimes to the extent of 90 per cent of specimens examined They have also been found infected in countries where few or no cases have been discovered, *e g* in Mexico, where recently a very few cases have been reported, and in California, Texas, and Arizona, where no case has yet been found Further, a trypanosome, apparently identical with *T cruzi*, has been found in nature in a large number, at least twenty, of species of *Triatomidæ* and many of these have been shown experimentally to be potential vectors

Other arthropods, *e g* *Cimex*, *Ornithodorus*, *Rhipicephalus*, have also been shown to be capable of maintaining the trypanosome in their intestinal canals, and of transmitting it

The infection is said to be transmitted from the adult bugs to their progeny in the ovum, but it is more likely that the larvæ are infected by the fæces of adults

Mechanism of transmission —The bug becomes infective eight to ten days after feeding, at any nymphal stage or in the adult stage, on an infected vertebrate, and retains the infection for the rest of its life, up to

two years The trypanosome multiplies and passes through different developmental stages to become a metacyclic, short stumpy, form which is passed in the fæces The salivary glands are

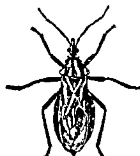


Figure 50 *Triatoma megista*

effected by but by the assed in the the wound made during the bite, and possibly by contamination of the conjunctivæ with the fingers The irritation caused by the bite will lead to scratching, so that either of these events is a likely sequel

d

e

opossum

Domestic animals are also found naturally infected, *e g* the cat and the dog, in a high percentage It seems probable that wild animals are the main sources of infection, as triatoma have been found living in their burrows

Cats and dogs are infected by feeding on infected rodents

EPIDEMIOLOGY

Geographical distribution —All the earliest cases were reported from the Minas Geraes district of Brazil, and in fact, as pointed out by Yorke (1937), only a little over a hundred cases had been reported from anywhere else up to that date, despite the very wide distribution of the infection in animals *and of the potential insect vectors* However, during the last few years more cases have been reported from many South American countries Argentina Uruguay, Peru Venezuela, and Chile from Panama, Guatemala and San Salvador, in Central America and recently from Mexico



Figure 51

No human case has yet been reported from the United States

After Brazil, Argentina has provided the largest number of cases, and this had reached about 500 by 1940 (Mazza) In most other countries only isolated cases have been found even after systematic investigation

Epidemic features —The disease is sporadic and occurs mainly amongst the infants and young children of the lower classes in the endemic areas Children of either sex are attacked and usually the first symptoms appear before they are two years old Older children and adults are occasionally affected The disease is commoner in country districts than in towns

PATHOLOGY

The type of lesion that is produced by the parasite is fairly constant, but the distribution amongst the organs and tissues of the body is very variable, this accounts for the diversity of the clinical manifestations

Cells in different parts of the body, mainly endothelial cells of the capillaries and lymphatics, and the reticular cells of other organs and tissues, are inv[illegible]
forms, multiply [illegible]
of cyst This c[illegible]
other organs and tissues

There appears to be an early brisk tissue reaction during the period of invasion, *e g* in the heart in a child who died within a few weeks of the first symptoms, there was an invasion of histiocytes and monocytes in the reticular tissue between the heart muscle fibres, but parasites were so scanty that only one or two were discovered, later, however, the local response to invasion appears to be very slight and large cyst-like bodies containing numerous multiplying leishmania forms are seen, with very slight reaction beyond a little fibrosis occurring in the surrounding tissues

The organs affected are mainly the heart, the brain, the suprarenals, ovaries and testes, the thyroid, the lymphatic glands, and the liver The parasite also has a predilection for skeletal muscles

Most of the chronic changes described have been in the thyroid, but it now seems very doubtful if these are really due to the trypanosome infection *(vide infra)*

In the heart, interstitial fibrosis of the myocardium, with parasites still present in a few cases only, is probably the commonest chronic lesion

SYMPTOMATOLOGY

As in most other infections by parasites of the family Trypanosomidæ the reaction to the infection is very variable, and it seems certain that many infections do not reach the clinical threshold In the few experimental infections the symptoms have usually been mild and temporary

An early acute and later chronic form of the disease are recognized

In the acute form which is nearly always in children, after an incubation period of 10 to 20 days, there is a sharp febrile attack of moderate intensity which lasts for about three weeks At the beginning of this attack, œdema of one side of the face may occur This œdema may spread to the neck, shoulders, chest, and arms, and in a few cases general anasarca has been reported This unilateral swelling of the face, which is usually most noticeable in the loose cellular tissue of the eyelids, is known as *Romana's sign* *The unilateral nature of this sign suggests that it is in* some way associated with the original point of entry of the infection, at the site of the bite, or *via* the conjunctiva, it does not appear to be the immediate reaction to the bite, but rather of the nature of a later allergic reaction when the general infection is established There is often a morbilliform rash on the arms and trunk

Other accompaniments of the acute attack are dyspnœa, cyanosis and other acute cardiac and cerebral symptoms *The liver is often enlarged* [illegible] lymphatic glands in the neck and other parts [illegible]
er a
child

About the chronic form there is considerable confusion in the litera-

If this view is accepted, there is little left of the chronic syndrome The patients who have been found infected, often accidentally and/or at post mortem, have shown a variety of symptoms, but the most commonly recurring ones are those associated with a chronic form of heart disease, with alterations in conductivity and disturbances in rhythm

Early death from chronic fibrotic changes in the heart is common in the districts where infected bugs are found, and, in the absence of any other obvious cause for this, and in view of the facts that many of these persons have been shown to be infected and that this trypanosome undoubtedly has a predilection for heart muscle, it is tempting to associate these two observations

Chagomas—This term has been introduced recently by Mazza to

after the primary lesion The inoculation chagoma appears within about a week of the inoculation and persists for some weeks, and leishmania forms of the parasite can be found in it

DIAGNOSIS

The clinical diagnosis in a typical case does not present any particular difficulties Romana's sign in children and the more recently described chagomas in both adults and children will arouse strong suspicion During the first few weeks of the infection, confirmation is not usually difficult, in a large percentage of cases, trypanosomes can be found in the blood, by direct examination or by the triple centrifugalization method (*see* p 210) The leishmania forms can also be demonstrated in the chagomas

Later, animal inoculation or xeno-diagnosis will be necessary

For the former, young animals, guinea-pigs or better still puppies, are inoculated with the deposit after triple centrifugalization of 10 c cm of blood from the patient After about 14 days, the trypanosomes will be found in the blood of the animal

Xeno-diagnosis is carried out by a
laboratory-bred triatoma to feed on a
secting the bug and demonstrating t
considered too elaborate a procedure fo
out, as a long-established laboratory strain of triatoma must be used in order to obviate a false positive finding

The Machado-Guerriro reaction is a form of complement-fixation test, in which an extract made from a heavily infected puppy's liver is used as antigen A more recent modification is to prepare a more standardized antigen from cultures of *T cruzi* in blood dextrose agar The test is said to be specific to a high degree at any stage after the early acute stage, it is not usually positive before the 30th day The result may however be *positive in sleeping sickness and kala azar, the latter disease occurs* in South America Both complement fixation and slide agglutination tests have been used and apparently give accurate results

PROGNOSIS

A high death rate is reported in the early acute stage in young children, the death rate is usually placed at about 50 per cent in the first year of

It must be remembered
cases, and, while it is
ways accompanied by
ildren and adults, for
ve been shown to be
suffering from a chronic infection

PREVENTION

The dark corners and the thatched roofs of the huts of the poor obviously ... any measure to improve the living ... d upon as a preventive procedure ... that mosquito nets, even of very w ... s should certainly be so protected

TREATMENT

None of the drugs so far used *in the treatment of sleeping sickness* has been of the slightest use in Chagas s disease

Mazza has reported very good results with Bayer 7602, a preparation
... ven intra-
olution in
per kilo-
Brumpt
have beer
so successful

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THE RELAPSING FEVERS

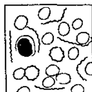
Definition.—Relapsing fever is an acute specific disease occurring in many parts of the world, characterized by fever that appears in bouts of a few days' duration, with a sudden onset, a rapid subsidence, and a tendency to relapse at regular short intervals, it is caused by a spirochæte that is found in the blood and in other organs and tissues, and is transmitted to man by insects of at least two genera. The symptoms vary with the genus of the transmitting insect.

Discussion.—Relapsing fevers that comply with the above definition have been described in many temperate, sub-tropical and tropical countries. The causal organism [illegible] shable from one another but have beer [illegible] generic and specific [illegible] by various workers —

Generic name	*Specific name*	*Location*	*Insect vector*
	recurrentis	Europe	*Pediculus humanus*
	obermeieri	Europe	
	carteri	India	
	novyi	America	
	ægyptica (um)	Egypt	
	berbera (um)	North Africa	
	duttoni	Central Africa	*Ornithodorus moubata*
	rossi	East Africa	
Spirochæta *Spironema* *Treponema* *Borrelia*	*kochi*	East Africa	*O savignyi*
	crocidurı	Africa	
	persica (um)	Persia and N W Africa	*O lahorensis* *O papillipes*
	sogdiana (um)	North Africa	*O moubata savignyi* and *erraticus*
	marocana (um)	Morocco	*O moubata* and *savignyi*
	hispanica (um)	S Spain	*O marocanus*
	neotropicalis	Panama	*O talje*
	venezuelensis (e)	Venezuela and Columbia	*O venezuelensis*
	turicatæ	Texas	*O turicata*
	normandi	North Africa	*O moubata savignyi* and *erraticus*

The confusion in the generic names is due to natural conservatism on the part of the clinician, which is not surprising in the circumstances, and to disagreement on the part of the parasitologist, mainly on the issue of priority, there is no suggestion that there is more than one genus concerned

[illegible] hand, carries with it
ent species in each of
justification for any
there are two species
concerned, *Spirochæta recurrentis* and *Spirochæta duttoni*, which are the causal organisms of the louse-transmitted and the tick-transmitted relapsing fevers, respectively, and that all the other names are synonyms *obermeieri carteri*, *berbera*, *ægyptica* and *novyi* for *recurrentis* and the rest for *duttoni*. As well as their morphology these two organisms have other common features but there are many differences that seem to justify their distinction into two separate species. In the clinical syndromes as well as in the epidemiologies of the respective infections produced by the spirochætes of these two species there are marked differences and they will be described separately


Figure 52 *Treponema recurrentis*

LOUSE BORNE RELAPSING FEVER

Historical —Rutty is given the credit for the first description of the disease
pidemic—and probably later—
y natural as the two diseases
oid bilious remittent malaria
ibed this epidemic in which
d Since this date there have
very frequently in association
lemics was usually recognized

EPIDEMIOLOGY

Geographical distribution —Relapsing fever has occurred in epidemic form at some time or other in almost every country in the world. During the last twenty years or so, it has occurred in eastern Europe—Poland, Russia, and the Balkans in Africa—in two belts divided by the Sahara desert, north Africa from Morocco to Egypt and central Africa from Senegal to Abyssinia, and in Asia—Turkey Syria, Iraq India (except Bengal and Assam), China and Indo China, Mongolia, and Asiatic Russia

It seems probable that it does not occur in Australia or in the East Indies. Western Europe, with the exception of Ireland has been free for some years, and no recent outbreak in America has been identified as louse-borne

Epidemic features —It is essentially an epidemic disease but cases that are apparently sporadic occur from time to time. Like most epidemic diseases it tends to occur in cycles, in this case the cycle has a 15 to 20-year periodicity. But it is certain that unnatural events such as wars, persecutions, poverty, and destitution, assist the natural events that determine the onset of the epidemics *e g* the epidemic in eastern Europe and western Asia during and after the 1914–18 war

Any country where the habits of the people are not naturally cleanly or where overcrowding and/or destitution are common is likely to suffer

epidemic outbreaks, and the disease is liable to spread to, and in, other countries and communities when normal standards are not maintained, during wars—amongst both troops and refugees—famines, and earthquakes and other natural disasters

A severe epidemic occurred in the African epidemic belt south of the Sahara (*vide supra*) from 1921 for about eight years, and affected some millions of persons, the death rate is said to have been about 5 per cent of the populations of these countries, and in some it was as high as 25 per cent In India, there has been little relapsing fever since 1929 when the last traces of the 1923-4-5 epidemic disappeared

Epidemic relapsing fever is very frequently but not only always associated with epidemic typhus, in a mixed epidemic the latter usually predominates

Seasonal incidence—There is a distinct seasonal variation in incidence, the height of the epidemic wave is usually in the spring In India and Iraq, the disease used to disappear completely during the hottest months of the year

Age sex race, and occupation—Relapsing fever appears to be most common in male adults, but persons of all ages and both sexes are susceptible Individuals of all races are susceptible unless protected by previous experience of the disease when a large percentage of the population is thus protected, racial immunity may be simulated

Washermen or -women, and dealers in old clothes are particularly liable to be infected Nurses and hospital attendants are also exposed
s, but not doctors, at least
spirochætes are not present
no air borne infection

ÆTIOLOGY

Historical—Obermeier first found the parasite in 1868 but he did not describe it until about five years later Lebert named it *Protomycetum recurrentis* in
ear the specific name *recurrentis*
untrie *e g* Vandyke Carter in
spirochæte and gave it different
was the important transmitter
in India, his observations were confirmed and extended by Nicolle Blaizot and Conseil (1913) in north Africa who showed that the transmission was not by the bite but by the crushing of the louse on the skin

The causal organism Morphology and staining—*Spirochæta** *recurrentis* is an actively motile spiral organism with five to ten fairly regular loose primary spirals, it is from 10 to 20μ in length and about 0 2μ in thickness, each spiral is 2 to 3μ in length and 1μ in amplitude The spirochætes can be seen, though not accurately, in a fresh specimen of blood preferably by dark-ground illumination They move by rapid

* The generic name *Spirochæta* is used here because it is still the most popular one
ies,
in
his
sm
ma
able
pertenue, an organism with regular short spirals (morphologically indistinguishable from the causal organism of syphilis) the cause of yaws *Treponema carateum*

rotation but not apparently purposefully for they move backwards and forwards within the space of the microscopic field

Culture—The spirochætes can be grown anaerobically in a medium containing ascitic fluid citrated blood and kidney substance but they do not grow well

Distribution and pathogenesis—They are found in the blood during the height of the febrile attack but disappear just before the fall of the temperature reappearing during the relapse It has been suggested that

tion
the
ætes
the

spleen and the brain where they can be found as such

Infection can be transmitted to a number of animals *e g* monkeys squirrels rats and mice but not to rabbits or guinea pigs In monkeys

less constant

n attack they
irochætes and
not last long
very complete
the antigenic
es they are is

of a much lower order than that between the various strains (or types) of *recurrentis* (*vide infra*)

tl at tl e immune
bodie to disappear into
the i isitory and when
they blood multiply
and l so on until the

antibody load is sufficient to knock out the infection altogether

In the writer s opinion the more feasible explanation is that there is a multiplicity of strains with slightly differing antigenic structures (*cf* the antigenic structure of Flexner dysentery strains *q v*) that when a person is infected he is infected by a number of strains of which one is dominant and causes the first bout of fever antibodies appear and suppress the spirochætes of this first strain spirochætes of another strain, hitherto dormant now appear and multiply and so on until eventually enough antibodies are formed to counteract spirochætes with all possible antigenic patterns This hypothesis is supported by the work of Cunningham and others (1934 *et seq*) in which he showed that in one individual the type' of spirochæte present in the initial attack was different from that present in the first relapse and that when a second relapse occurred a third type appeared and so on The type recoverable during the apyrexial period was always the type that appeared in the *next* paroxysm He separated

nine antigenic types (as he called them) four of which were stable types maintaining their antigenic individuality through many sub passages but the other five tended eventually to revert to one or other of the four stable types

Transmission—This is effected by the louse *Pediculus humanus* After the louse has fed on an infected person the spirochætes disappear in about 24 hours and are not traceable in the louse nor is it infective for another three to five days, after this they reappear as slender metacyclic forms in the fluid of the body cavity of the louse and can be found in all parts of its body (they are easily demonstrated by taking off a leg and making a smear from the exuding fluid) the louse remains infective for the rest of its life Transmission occurs when the louse is crushed and the body cavity fluid rubbed into the abraded skin *The bite of the louse does not transmit infection nor do its fæces* It is a question whether infection can be transmitted through the unbroken skin by the blood or

Source and spread of infection—Whilst man is not the only susceptible
on man so that man must

spirochæte of *endemic relapsing fever* (*vide infra*) might provide the initial infection for a louse borne epidemic It has been shown that it is possible to infect lice with this organism and it is conceivable that after several passages through the louse the spirochætal strain might undergo some biological change so that it behaves like or actually becomes *Spirochæta recurrentis* The infection is spread by direct contact with the body of a louse infected patient by handling his louse infected clothes or by louse interchange during close contact and it may be conveyed considerable distances in louse infected clothes

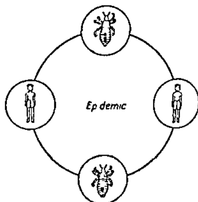


Figure 53 The transmission cycle in louse borne relapsing fever

PATHOLOGY

Morbid anatomy—The large majority of the patients who die from this condition die from some secondary infection and the true pathological picture is hard to gather

and mucous membranes are
jaun emorrhages The liver and
splee

The most constant lesions are in the spleen this organ is enlarged and soft and shows many miliary necrotic lesions especially in the

reas of congestion and cell infiltration
which spirochætes will be found inside

In the bone marrow there is marked leucoblastic hyperplasia

In the other organs, in the liver and kidney, there is cloudy swelling and degeneration of the parenchyma cells

Blood picture —There is usually a distinct polymorphonuclear leucocytosis, with an actual increase in large mononuclears also Counts of about 12 000 to 15 000 per c mm are usually found This is not a constant finding

Reference to the presence of the spirochæte in the blood has been made above (*see* also Diagnosis)

Urine —Slight albuminuria will be found in more than half of the cases, and often granular casts, in severe cases there may be hæmaturia

SYMPTOMATOLOGY

The incubation period is from three to seven days as a rule, the limits being from 2 to 14 days (In experimental infections it has always been between two and six days)

perature rising to
are often severe
articularly severe
The skin is hot
The eyes show
ated but usually
the onset is not
unusual and may be a marked feature of some severe epidemics

An erythematous rash appears early in the first febrile attack in perhaps less than half the cases In severe cases this may become petechial and even hæmorrhagic It appears to start from the tip of the mastoid process and it spreads out over the neck shoulders arms back and chest

Frank jaundice occurs in 20 to 50 per cent of cases in different epidemics it appears early

Both spleen and liver are enlarged in the majority of cases, the latter will usually be tender The splenic enlargement is only slight and may disappear between attacks The first attack usually lasts five or six days but occassionally it will be prolonged even up to 12 days the crisis then occurs and the patient s temperature drops to sub normal with profuse sweating and in severe cases with considerable prostration Heart failure at this stage is not uncommon Cases have been reported in which the temperature fell 10°F in a few hours



Figure 54 Temperature chart in louse borne relapsing fever (original)

of the first attack to the onset of the first relapse is constant for each type of

days, average 13 days This vie

The first relapse is seldom as severe or as long as the initial attack but is otherwise very similar to it After another interval usually shorter than the first, in the writer s experience there may be a second relapse which will again be shorter and less severe than the first

In this form of the disease there are never more than four relapses *The following figures have been given for the number of relapses that occur* in different epidemics —

A single attack	10 to 50 per cent
One relapse	25 to 50
Two relapses	10 to 40
More than two relapses	1 to 2

Complications and sequelæ—Cough and *bronchitis are so common in* temperate climates that they may be looked upon as a constant feature of the disease They are less common in the tropics Broncho pneumonia is a relatively common complication in cold climates

In pregnant women abortion will usually occur Eye complications are not uncommon particularly in a mal nourished population these in clude iritis and ophthalmia

Parotitis nephritis polyarthritis and neuritis are rarer sequelæ the latter is very rare in this form of the disease though common in tick borne relapsing fever

DIAGNOSIS

While the complete temperature chart of a case of relapsing fever is so characteristic that one could scarcely fail to recognize it it must be

In most epidemics the parasites are easy to find but are easily over looked if not specifically looked for

Giemsa s or Leishman s stains will show up the spirochætes very well In looking for malaria parasites one focuses *on* the red cells and not *between* them so that unless one expects to find spirochætes it is very easy to miss them even in a well stained film The curious circular form that they may take simulates a rather pale red cell but if one examines these forms *carefully the disguise is easily penetrated*

It should be remembered that the spirochætes disappear from the peri pheral blood 24 hours before the crisis They will not be found during the remission period and are usually scantier in a relapse than in the initial attack

Differential diagnosis—At the height of the attack influenza dengue
ven small pox may be
e mistaken for dengue
usually very slow

PREVENTION

Preventive measures will consist in keeping the populations in a louse free condition in preventing conditions that will encourage an interchange of lice (*e g* overcrowding) in the early hospitalization and treatment of all cases and in instituting special measures for delousing all patients admitted to hospital during an epidemic

Established lousiness will never be tolerated by an educated and sane individual, in ordinary circumstances, and its prevention is solely a matter of personal cleanliness

The clothing of hospital and ambulance personnel should be white, one-piece, and with no openings in front (figure 55), gloves and gum-boots should be worn and the sleeves and trousers tied firmly round the wrists and ankles, a white handkerchief tied round the head, covering the hair, and a gauze mask worn across the mouth and nose For

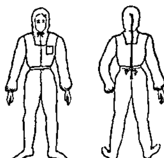


Figure 55 Figure shows one piece suit for use by ho pital and ambulance personnel It is closed by means of a zipper behind elastic round the wrists and a tape round the face tied under the chin

where typhus is also suspected For ho pital personnel the best protection that can be given is the complete delousing of the patients before admission

will however necessitate complete removal of all hair from the body and in the case of men it will be advisable to include the head, followed by thorough washing with antiseptic soap under supervision Women will usually object to having their heads shaved and an elaborate process of hair washing is necessary

mixture is —

Kerosene	50 per cent	Citronella oil	1 per cent
Tar oil	5	Coconut oil	44

Coconut oil alone will not destroy lice though it may gum up the ova and prevent hatching to some extent

A much more effective method of which the writer has had recent first-hand experience, is by spraying the hair thoroughly with a pyrethrum and kerosene mixture The patient should be given a small towel to hold over her face, the hair is then sprayed thoroughly from all directions with a no 15 de Vilbiss atomizer, care being taken that the lotion reaches all the roots of the hairs

The lotion is made with one part of 'pyrocide 20 , or any other concentrated pyrethrum extract and 19 parts of white kerosene or deobase oil which is scentless To this a little (one per cent) of citronella oil may be added to give the lotion a smell, but it is not necessary

Underclothing removed
and other clothing autocla
autoclaving, a comparativel
minutes will kill lice and
boots and other clothing tha
for 2 hours to 0 2 per cent
this

Repeated inspection of the clothing of personnel, especially the menial personnel, of a hospital is an essential measure to maintain freedom from lice A lens will facilitate the search for lice and their eggs, special attention should be paid to the seams of the underclothing

For the delousing of troops or infested populations, a very well-organized delousing station is necessary This must include an entrance room for undressing, with side rooms for dirty underclothes, the disinfestation of outer clothing, and the safe-keeping of money and other valuables, from this room the individual passes through the barber's room, the washing room, and the medical-inspection room to the dressing room where he is issued with clean under-linen, and receives back his outer clothing and valuables

The introduction of DDT has simplified delousing, a 10 per cent powder in pyrophyllite and 6 per cent spray in benzyl-benzoate being convenient forms Clothes can be rendered louse-proof for several weeks by impregnation with a 2 per cent emulsion

TREATMENT

The general and dietetic treatment will be that of any short febrile disease It is not necessary to force food during the febrile period, but a fluid diet of about 1,000 calories with plenty of additional fluid will be sufficient The calorie intake may be doubled during the intermission, but the patient should not be given the free run of his teeth during this period as he may be ravenously hungry The diet at this time should be well balanced and still mainly fluid

Rest in bed is important, it will be observed naturally during the febrile attacks, but the patient should be warned seriously of the danger of collapse and heart failure during the early intermission period

Mouth sanitation should be given special attention

Specific treatment—The arsphenamine preparations have a rapid specific action Novarsenobillon has proved the best drug in the writer's experience, but any of the well-known preparations can be used A single dose of 0 6 gramme for a normal male adult, and a smaller dose in others on the basis of about 0 01 gramme per kilogramme body-weight should be given, a second dose is seldom necessary and should only be given if a relapse occurs

... the first three or four days of the
will be as well
ven just before
metimes follows
f the cases no
relapse occurs it may be possible to dispense with the specific treatment altogether This may be important in an epidemic when cost and/or the supply of drugs have to be considered, arsphenamine can in such circumstances be reserved for severe cases only

... on this infection in animals (Augustine
(21 million units) is too large

PROGNOSIS

After one adequate dose of arsphenamine the relapse incidence will not exceed 15 per cent

The death rate varies very considerably from epidemic to epidemic, and according to the circumstances Figures from 1 to 50 per cent are quoted, but the latter high figure would only occur in a starved or exhausted population

TICK-BORNE RELAPSING FEVER

fever in Africa was conveyed
ig of the spirochæte in African
lefinitely showed that infection

Later other workers discovered other transmitters of the disease in other countries (see p 224)

EPIDEMIOLOGY

Geographical distribution — This form of the disease has a typically

Brazil and Argentina in Mexico and a number of western and mid west states of the U S A, California, Colorado, Arizona, Texas, and Kansas

Epidemic features —It is essentially an endemic disease and it occurs sporadically in the countries mentioned above Children are very likely to be infected whilst playing on the ground, as thereby they come into closer contact with the ticks It is a regional or even a house infection, a history of a succession of infections amongst visitors to a house has often been obtained

Temperature is an important factor controlling the development of the spirochæte in the tick In tropical countries, the disease is perennial, but in the sub-tropics, cases occur mainly in the spring and summer, when the ticks are always most active

ÆTIOLOGY

The causal organism as has been stated above, is morphologically identical with *Spirochæta recurrentis*

Transmission —It is believed by some workers that *S duttoni* was originally a parasite of *Ornithodorus moubata* and that man was only infected incidentally, there is evidence that once infected, *O moubata* is capable of maintaining the infection through many generations, if not indefinitely, and transmitting it to man so that the cycle of infection is as shown in figure 56 However, clean ticks may become infected through feeding on an infected man The spirochætes are taken into the insect's gut with the blood meal, after disappearing for a few days, they reappear and invade practically all the tissues of the insect host They are found in large numbers in the body cavity fluid, where they multiply The

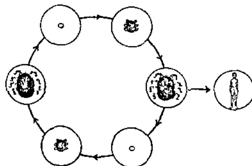


Figure 56 The transmission cycle in African (*moubata*) tick borne relapsing fever

spirochætes enter the body cells, including the cells of the ovaries, and are transmitted to the next generation through the ovum

In the case of the other vector ticks, *Ornithodorus erraticus*, for example, the infection dies out after passing through two or three generations, and the tick only becomes reinfected after feeding on an infected mammal Unlike *O moubata*, that feeds on man only, these other ticks feed on their natural *hosts, rodents and small* carnivores, which act as reservoirs of infection, and they transmit the infection to man sporadically (*see* figure 57)

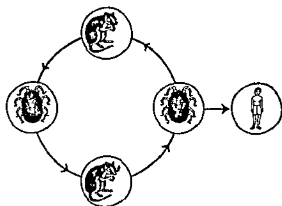


Figure 57 The transmission cycle in other tick borne (*e.g erraticus*) relapsing fevers

The actual method of transmission is a matter of *controversy, but, as diverse* results have been obtained by reliable workers using different vectors it is more

of
a
orc
e

mission will take place by each one of some ticks transmission will be by more three, Buxton (1939) believes that in *O moubata* the coxal fluid is the only *medium of infection It seems very unlikely that, in nature, transmission* would take place by the tick being crushed on the skin, ticks are far too tough for this, though experimentally it is possible to cause infection in this way

a feed normally
, weasels, foxes
have been found
k, transmits the
ured by picking

PATHOLOGY

The pathological lesions are very much the same as in louse borne relapsing fever, but this spirochæte shows a greater tendency to attack nerve tissue In experimental infections in mice the spirochætes can always be recovered from the brain, the clinical evidence of this neurotro*pism is the frequency* with which neuritis and paralyses occur as a sequel

The **blood picture** is the same as in the louse-borne infection, the spirochætes are usually scantier, and the thick drop method may have to be adopted to find them A positive Wassermann reaction appears *to* occur in this disease in 10 to 20 per cent of cases, irrespective of syphilitic infection

SYMPTOMATOLOGY

In each different relapsing-fever area, the disease shows a somewhat different picture, only the special features of the various types, *as they*

differ from the louse-borne infection, as well as from one another, will be indicated

The special features of the African type are —

The incubation period tends to be slightly longer, seven to ten days, the febrile period may be much shorter, lasting only a day or so, but in some cases, the fever lasts four or five days and shows deep remissions The 'afebrile' period is usually about seven days but is very variable, in some cases it is only a day or two, and in others up to two or three weeks The temperature during the remission ('afebrile' period) seldom remains quite normal but is irregular, frequently rising to 99 5°F or 100°F Occasionally, the fever loses all its relapsing character and becomes intermittent

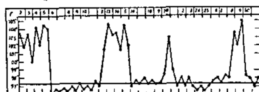


Figure 58 Temperature chart in tick borne relapsing fever (original)

The relapses are far more numerous as many as eleven have been reported

In some outbreaks, fulminating cases occur in which there is severe jaundice, hæmorrhages, and coma, and the patient dies within 48 hours

The common complications are bronchitis and pneumonia, as in the other forms of relapsing fever, but in tick relapsing fever, the special sequelæ are diarrhœa and dysentery, neuritis, spastic paralyses, aphasia strabismus, deafness, hemiplegia, and fortunately very rarely, atrophy of the optic nerve Parotitis and iritis also occur The cerebrospinal fluid may be under increased pressure in it, spirochætes are sometimes found, and there is usually an increase of lymphocytes

In the **Iranian type** the disease is milder, the initial pyrexial bout usually lasts four or five days, there may be deep remissions, and there are a number, usually four or five, relapses of much shorter duration, not usually more than three days The attack is usually relatively mild, but severe attacks have been reported

The **Spanish type** is also mild, but the patient is very drowsy, and prostration may be considerable when the temperature falls Herpes labialis is common The spleen and cervical lymphatic glands are enlarged

There are not usually more than four relapses

The leucocytosis occasionally amounts to 25,000 per c mm

DIAGNOSIS

The clinical diagnosis will be more difficult than in louse borne relapsing fever, and the fever will often simulate malaria The spirochætes also may be more difficult to find in the blood film and thick films should be examined (*see* p 87), but animals are more easily infected with *Spirochæta duttoni* than with *Spirochæta recurrentis* in mice the brain should be examined for spirochætes

PREVENTION

The preventive measures to be adopted against this disease must obviously be very different from those employed against the louse-borne infection, however, the possibility that the spirochæte may change its habitat and become adapted to living in the louse should not be forgotten,

and lousiness should be looked upon ... area of tick-borne relapsing fever ... against *Ornithodorus moubata*, beca... floors of native huts and even European houses Old heavily infected huts or houses should be demolished preferably by burning, and replaced by buildings with concrete floors and well-built brick walls Other houses it may be possible to repair and to make tick proof

The sites of camps must be carefully selected, and old camp sites and areas near villages avoided

Sleeping on the floor should be discouraged but old locally-made beds should be avoided

In the case of other tick vectors preventive measures will be difficult since they live in the caves and burrows of their alternative hosts and only come into man's habitations fortuitously The control of domestic animals *that may bring them in will be an important preventive measure*

For personal protection suitable clothing that will protect from ticks *should be worn in 'tick country'* *After walking in bush or jungle the* legs should be examined any adhering ticks removed carefully and the area from where they have been removed washed with a strong antiseptic The starved tick does not transmit infection for some hours The tick must not be pulled off, but touched with a hot cigarette end or some strong *insecticide to make it loosen its grip*

TREATMENT

This is not materially different from that of the louse borne relapsing type (*q v*) However, since in most of the tick borne types, relap es are *far more* numerous specific treatment will be indicated whenever it is available The infection is more resistant to treatment, and the injections will often have to be repeated

PROGNOSIS

The average death rate is about 6 per cent Some types are very mild but from time to time a fulminating outbreak of the African type occurs with a death rate of at least 50 per cent

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RAT-BITE FEVER

Definition.—Rat bite fever is a fever of relapsing type caused by micro organisms that are conveyed to man by the bite of small animals mainly rats

Discussion.—All recent evidence suggests that the parasite principally responsible for this disease is the spirochætal micro organism *Spirillum*

minus _ However, the careful work of Schottmüller (1914) and others wh
mals inoculated with the blood o
ver cannot be ignored, and recen
it may be the commoner causa

and Das Gupta (1928)
fever in which they had
every other case they found the latter organism, and from this they con-
cluded that, in India at least, *Spirillum minus* is the sole causal organism and that the presence of a streptobacillus was an accidental association The disease caused by *Spirillum minus* will be described here

Historical —The disease has been recognized, in Japan and elsewhere, as a clinical entity for many years, in Japan it was known as *sodoku* (*so* = rat, *doku* = poison) In India, the first clinical record was in 1913 However, the discovery in *1916* by Futaki and others, of the causal organism gave the disease a more concrete form

EPIDEMIOLOGY

Geographical distribution —This is probably world-wide, but the tropical association of the disease is not solely a matter of poor sanitary and social conditions, though these undoubtedly play an important part, climate *per se* is probably a factor Most of the earliest cases were reported from Japan Knowles and Das Gupta (1928) drew attention to the fact that it was a common disease in India and certainly in Calcutta, and the subsequent annual reports of the School of Tropical Medicine have borne this out, between 50 and 100 cases are seen annually at the out-patient department of the School

Isolated cases have been reported from many countries The first definite report of a case in the United States was made by Shattuck and Theiler in 1924, and Bayne-Jones (1931) collected 75 apparently authentic cases from the literature, *Spirillum minus* had been isolated in only five of these cases



Figure 59 Seasonal incidence of 455 cases of rat-bite fever in Calcutta between 1931 and 1936
(*Chopra Basu and Sen 1939*)

Epidemic features —It is essentially a sporadic disease, it occurs in those living under insanitary conditions and most subject to the bites of rats, the published records of age and sex incidence reflect only the age distribution of the population from which they are drawn, but there
... be a definite seasonal inci-
... ls
... ie
year (*see* figure 59)

ÆTIOLOGY

Historical — *The causal organism was first reported upon by* Vandyke Carter in 1887 in India he found it in the blood of rats but did not associate it with the disease Others reported a similar organism found in other rodents but Futaki *et al* (1916) were the first to associate it with the disease and isolate it from an infected patient They named it *Spirochæta morsus muris* The organism differs from the true spirochætes in possessing flagella, and its correct name is *Spirillum minus* [The streptobacillus isolated by Schottmüller (1914) and later by others (*vide supra*) cannot, in the opinion of Topley and Wilson (1938), be ignored as the possible cause of a similar form of fever but the *Spirillum minus* infection undoubtedly has a more tropical distribution]

The causal org measuring from 2

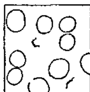


Figure 60
Spirillum minus

dark ground illumination, the rapid, darting, and progressive movements of the organism can be studied, these movements are effected by means of terminal flagella—of which there are several at each pole—and are very different from the backward-and forward movements of the spirochætes Multiplication takes place by transverse division

The spirillum stains well with Giemsa's or other Romanowsky stains, but for demonstrating the flagella Tribondeau's modification of Fontana's silver impregnation method is perhaps the best The spirilla can be shown in the tissues by this method

Cultivation of the organisms has been claimed by Futaki and others, but it is not at present a practical procedure

The infection is readily transmissible to laboratory animals monkeys, guinea-pigs rats and mice, the last-named are most commonly used It has been claimed that the infection is transmitted from the mother to the young, either by intra uterine or by milk infection Das Gupta (1938) however failed to confirm this observation as also to infect mice by feeding them on contaminated food Nevertheless it is not uncommon for one's whole stock of laboratory mice to become infected naturally

Distribution in the tissues—In man the spirillum is found in the local tissues at the site of the bite, in the lymphatics draining the area in the lymph nodes on the course of these, and in the blood It has also been demonstrated in the liver spleen, kidney and suprarenals

In animals, it appears in the blood in about six days, and it has a predilection for the connective tissues of the nose, the lips, and the gums Infection of the conjunctival sac is apparently common, the organisms being found in the secretions *The salivary glands are not infected*

Transmission—This is effected by the bite of an infected rat or other small animal The tissues around the mouth are particularly

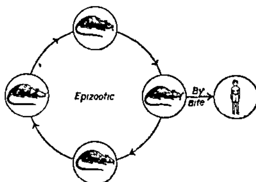


Figure 61 The transmission cycle in rat bite fever

...usly it usually damages its gums ...ntaminates the wound Another ...is infected by the conjunctival

Animal reservoirs of infection—Wild rats constitute the main reservoir, 3 per cent of wild rats in Japan have been shown to be infected In

Calcutta, infected rats have frequently been found After the rat, the cat is the most common agent of infection, and instances have been reported of a similar disease following the bites of weasels ferrets, squirrels (Das Gupta, 1942), and even dogs, it will be noted that most of these are carnivores that habitually kill rats and are likely to have been infected by rats when they were killing them As infection is apparently not transmissible by the oral route, it is uncertain how it is transmitted from rat to rat

PATHOLOGY

Locally, there is hyperæmia and œdema of the skin and subcutaneous tissues, with polymorphonuclear and eosinophil infiltration Similar changes will be found in the lymph nodes that drain the area

Hyperæmia
and the tubular
epith yma cells in
the centre of the liver lobules, have been described

In the rat, there appears to be little tissue reaction to the infection The liver may show some congestion In mice, there may be conjunctivitis and loss of hair Young guinea-pigs usually show emaciation, keratosis, and other eye complications, and die within two months

Blood picture—There is an increasing anæmia if the disease is allowed to progress untreated but this is not very evident in cases in which treatment is instituted early With the onset of fever, there is a sharp rise in the leucocyte count, which subsides during the remission periods there is a relative increase in eosinophils and a decrease in lymphocytes

Urine—A cloud of albumin is common and, more rarely, granular casts appear

The Wassermann reaction is reported to be positive in this disease Our experience in Calcutta contradicts this Das Gupta chose Wasser-
experimentally with *Spirillum*
Wassermann reactions become
Kahn reaction is frequently
on is negative, the writer has

SYMPTOMATOLOGY

A definite history of a rat bite may be given, but, as the majority of bites occur at night much more frequently the patient says that he was awakened by a sudden pain in his foot or hand, and that next morning he found an inflamed local lesion which was obviously a bite

The incubation period is very variable, but the average is about two weeks, instances as short as three days and as long as several months have been reported The initial lesions made by the bite may heal in a few days, this will depend on the degree of sepsis Then, after the incubation period, the true onset will occur suddenly with a high rise of temperature and often a rigor, headache, pains in the joints and muscles, and a considerable degree of prostration With the first and sometimes with each subsequent febrile paroxysm, there is a local response of the allergic type with redness, swelling and œdema at the site of the original lesion, and, if this has not healed, there will be an increase in the amount

of discharge The reaction may also occur in the proximal lymph nodes, which were possibly swollen previously but had meanwhile subsided

At the same time a rash may appear on different parts of the body,

relapses

The rash is by no means common, it occurs in less than 2 per cent of our Calcutta cases

The fever rises sharply to 103° or 104°F and may remain as a high remittent temperature for three or four days, it then falls to normal within a few hours, where it remains for a variable period but not usually more than a week (*see* figure 62) The second rise of temperature is usually as high as the first but the duration is shorter, if no specific treatment is given these **relapses** may occur at intervals of from 6 to 10 days for many months, but, as a rule the febrile paroxysms become less and less in height and duration, and eventually the infection disappears spontaneously

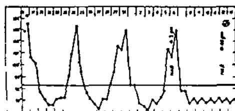


Figure 62 'Rat-bite fever after a bite by a squirrel (Das Gupta 1942)
A classical temperature chart of rat bite fever showing regular periodicity and response to arsphenamine

The rhythm of the paroxysms may be disturbed by sepsis, and the temperature may show a moderately high, irregular curve in which the paroxysms are scarcely distinguishable (see figure 63)

DIAGNOSIS

A clinical diagnosis can often be made on the history alone, definite or circumstantial evidence of a rat bite which healed in a few days, an interval of about a fortnight, and a sudden attack of fever with a focal reaction, even before the relapsing nature of the fever with its characteristic periodicity (longer than malaria and shorter than relapsing fever) becomes apparent, are sufficient to establish a diagnosis with a considerable degree of certainty

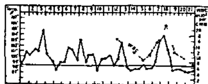


Figure 63 Temperature chart and leucocyte count in rat-bite fever

There are three practical **laboratory methods** of confirming the diagnosis (*a*) by direct examination of serous exudate taken from the initial lesion, (*b*) by the immobilization test with the patient's serum and (*c*) by animal inoculation with exudate or blood

(*a*) **Examination of local lesion** —The hyperæmic or œdematous area around the site of the bite is pricked with a sterile needle, after sterilization

of the area and subsequent washing with normal saline, and the exudate

characteristic shape, as well as by its movements, now slowed down.

Films made from the exudate stained by Leishman's or Giemsa's stains will often show the spirilla quite well, but Tribondeau's modification of Fontana's stain gives the best results, the technique of this method is described by Das Gupta (1938) as follows —

(i) A thin film of the clear serous exudate is prepared from the lesion on a clean slide and allowed to dry in the air

(ii) The slide is [illegible] with Ruge's solution, which has the follo[illegible] 1 c cm solution of formaldehyde 2 c cm [illegible] fixative is poured on and drained off, thi[illegible] bout a minute

(iii) The fixative is drained off the slide which is next covered with methyl alcohol and flamed by applying a lighted match This completes fixation

(iv) The slide is laid on the staining rack and flooded with the following mordant tannic acid 5 grammes, in distilled water, 100 c.cm It is gently warmed until steam rises The best and least messy way of doing this is to wrap a little cotton-wool round the end of a piece of wire, soak it in alcohol light it and hold under the slide When steam rises from the slide the flame is removed and the mordant allowed to act for thirty seconds longer without further heating

(v) The slide is washed with distilled water and then covered with Fontana's silver solution To prepare this a 5 per cent aqueous solution of silver nitrate is taken in a glass cylinder which has previously been thoroughly washed with distilled water With a capillary pipette a strong solution of ammonia is added drop by drop A sepia precipitate forms and then re-dissolves To the now [illegible] carefully, and only drop [illegible] which is just opalescent [illegible] silver solution should be [illegible] The slide is covered with [illegible] the flame is removed [illegible] thirty seconds

(vi) The film is washed in distilled water and allowed to dry in the air It should never be blotted

The film is then examined with an oil immersion lens The spirilla are stained an intense brown black or black against a faint yellow background

The spirilla are usually scanty and a determined search for them has to be made they were found in 64 per cent of our Calcutta cases believed on clinical grounds to be cases of rat-bite fever

(*b*) Immobilization of spirilla with patient's serum —Blood is taken *from an infected mouse's tail and mixed with a 1-in-5 dilution of the* patient's serum in normal saline A coverslip is applied and the specimen sealed with vaseline Examined after an hour, the spirilla will be immobile if the patient is suffering from rat-bite fever, but still very active in the [illegible] positive [illegible] exclude

(*c*) Animal inoculation —The most suitable animals are —(i) *White mice* the limitation is that those animals are very subject to 'natural' infection, so that clean stock has to be used and the mice examined thoroughly before inoculation (ii) *Young guinea-pigs* in these the development of the infection is slower and perhaps less certain (iii) *Other animals* these include adult guinea-pigs, rabbits and monkeys

The inoculation is made either from the serous exudate from the lesions, a drop of which is given subcutaneously, or from the blood, 0 5 c cm being given intraperitoneally to a mouse, 1 c cm to a young guinea-pig, and 2 c cm or more to any of the larger animals used

Spirilla were identified in 70 per cent of our clinically typical Calcutta cases by blood inoculation into white mice

Therapeutic test—One adequate dose of arsphenamine will always interrupt, at any rate temporarily, the periodicity of the fever

Differential diagnosis—The conditions likely to be confused with rat-bite fever are—

(i) Septic fever from the bite this will usually follow the bite almost immediately

(ii) Filarial lymphangitis and fever microfilariæ will usually be found in the blood taken at night

(iii) Relapsing fever the 'disease period' is usually much longer, and spirochætes will be found in the blood

(iv) Malaria the periodicity is much shorter malaria parasites will be found in the blood and the fever will respond to anti-malarial drugs

Rat-bite fever may simulate other short febrile diseases, such as dengue sand-fly fever, and influenza, but the diagnosis will be cleared up when the characteristic periodicity of the fever becomes apparent

TREATMENT

The prophylactic treatment of a rat bite consists in applying pure phenol to the wound with a match stick swab, washing this out with sterile water, putting powdered sulphanilamide into the wound, and applying a dressing

Specific treatment is provided by any of the arsphenamine group of drugs given according to the weight of the patient (see p 232) Usually two injections will effect a complete cure, but it may be advisable to give a third

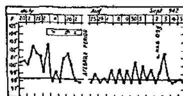


Figure 64 Sulphapyridine appeared to effect a cure but *Spirillum minus* was still present in the blood and the fever relapsed

Sulphapyridine given in the usual doses appears to control the fever temporarily in some cases, but it does not effect a cure In the case of which the temperature chart is shown in figure 64 spirilla were found in the blood until novarsenobillon was given

PROGNOSIS

If adequate treatment is given, complete recovery may be expected by the time the local lesion settles down and the death rate in our experience has been negligible In Japan, however, a death rate of 10 per cent has been reported

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LEPTOSPIROSIS

... l name 'leptospirosis' are grouped have many common clinical and caused by organisms of the genus Weil's disease or infective jaundice, ıpan, but there are probably many other similar but distinguishable syndromes which are as yet not clearly differentiated

Leptospira is the generic name of a group of spirochæte-like organisms, they have tightly-wound spirals, which give them the appearance of a twisted rope, and, usually, hooked ends They live saprophytically as well as parasitically The commonest species is *Leptospira biflexa*, which is found in water supplies in many parts of the world and is a filter-passer The parasitic species infect rodents and man causing in the latter diseases of the group under discussion

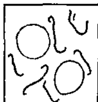


Figure 65
Leptospiræ

WEIL'S DISEASE OR INFECTIVE JAUNDICE

Definition —Weil's disease is an acute infectious disease of sudden onset, characterized by fever, jaundice, albuminuria, hæmorrhages from mucous surfaces, extreme prostration, muscular pain and tenderness and occasionally a petechial rash, it is caused by a spirochætal organism of the genus *Leptospira*, which is a common infection of the urinary tract of rodents and which infects man through abrasions in the skin and mucous membranes, or by the oral route

Historical —Infective jaundice is not a new disease Early in the nineteenth century French writers described the disease and reported small outbreaks of it in Europe In 1886 Weil gave a clear description of the disease and from that ... history, ... ly more ... ver in ... tospiral ... Weil's disease and it was soon shown to have a widespread distribution

EPIDEMIOLOGY

Geographical distribution —It occurs in Japan Holland, Great Britain, France, Germany, Sweden, ... ing countries In Japan, about ... Great Britain about 100 cases, in ... European countries a varying number, probably more or less in proportion to the amount of attention that is paid to the disease During the 1914–18 war, the disease was common among the troops serving on the Western front So far as India and her immediate neighbours are concerned, a small number of cases have been reported from time to time by different workers from several places such as the Andamans (Barker, 1926), Rangoon, Calcutta Bombay, Madras, and the North-West Frontier Province In most of these places the disease occurs in a sporadic form For example, in Calcutta within the last seven years some 50 or more cases have been reported In the Andamans, a sharp outbreak occurred in 1929 in which less than a hundred cases were recorded, but now that its presence has been recognized a large number of cases have been diagnosed each year

Epidemic status —On account of the very low incidence, the disease is not at present one of very great public health importance in any tropical

country with the possible exception of the Andaman Islands but there are indications that it may be much more widespread than it appears to be at present

In temperate countries its occupational character stands out so clearly that it comes within the purview of workmen s compensation acts It occurs in those who come in contact with water or slime contaminated with the urine of infected rats Sewer and canal workers miners fish handlers and butchers agricultural labourers sugar-cane cutters bargemen and soldiers fighting in trenches are liable to suffer from it

In the Andamans the diseases is found chiefly amongst agricultural labourers many of whom are adult males who have to work standing in water during part of the year However in Calcutta Das Gupta who has confirmed the diagnosis in 40 to 50 cases during the last few years found no association with any particular occupation Moist soil moderate temperature insanitary conditions and rat infestation favour incidence In cities sporadic cases may occur amongst the general population The larger outbreaks are generally confined to swampy areas to mines and to canal and coastal regions but even in the largest outbreak the number of cases is never more than a few hundred

Seasonal incidence — In cooler countries it is a summer and autumn infection but in the tropics the disease occurs most frequently during or after the rains and with the onset of dry cold weather it tends to disappear

Race sex and age incidence — It occurs in people of all races and in both sexes but few cases have been reported amongst children The majority of the occupational groups have consisted of men only but in the case of the fish handlers they were mostly women

ÆTIOLOGY

The causal organism —*Leptospira icterohæmorrhagiæ* is a spiral organism 6 to 9μ long and 0 25 [illegible]
wound spirals which g[illegible]
hooked It is actively
illumination It grows
or Vervoort s medium but takes a week to grow

Serological strains — There are a large number of serological strains of leptospira known Of these at least three strains have been recovered from the cases occurring in India Whilst there is a tendency towards a geographical grouping of these strains in the same outbreak more than one strain may be isolated The *canicola* strain is common in the United States

Resistance —*Leptospira icterohæmorrhagiæ* is a comparatively hardy
[illegible]

in ten minutes

[illegible] a blood infection during
period leptospiræ will be
e liver spleen and kidney
and the kidney becomes

balance of evidence is, however, in favour of the rat's playing some essential part in the transmission of the disease to man

Route of entry—The organisms enter either by the **mouth** or through the **skin**. The latter is considered to be the more frequent route of entry. Organisms generally enter through abrasions in the skin, though they are capable of penetrating even the unbroken skin and mucous membrane. Prolonged contact with infected water and soil facilitates entry. Bathing and accidental immersion in infected water have frequently given rise to the disease, and in Holland it is the commonest mode of infection

Immunity—From the sporadic nature of the incidence of the disease, even in the presence of a heavy source of infection, it would appear that man enjoys some natural immunity against leptospira infection. After recovery from an attack of the disease, a high degree of immunity develops. This acquired immunity is mainly due to the presence of specific antibodies. Convalescent serum has therefore been used in treatment (*vide infra*), as well as the serum of immunized horses, which in some countries has been used extensively. Active immunity can be produced in man by means of a specific vaccine. Das Gupta (1942) found that after inoculation, antibodies protective to guinea pigs appeared in the blood but disappeared within a year

PATHOLOGY

After an initial leptospiræmia, toxins produced by the leptospiræ dam

[illegible]

Morbid anatomy.—The **liver** is enlarged and usually yellow, there is degeneration of the parenchyma cells which will vary from degeneration of isolated cells, to similar changes in localized areas, and to complete disorganization of the whole liver structure, similar to, but usually not so extensive as, the changes that occur in yellow fever. Where isolated parenchyma cells are affected, they die, but are replaced, so that, unless the damage is very extensive, complete recovery is possible

In the **kidneys**, there is invasion of the inter-tubular tissues where small hæmorrhages occur, and degenerative changes occur in the tubular epithelium, regeneration follows in the latter case, but the interstitial changes will sometimes, though rarely, lead to a chronic nephritis

The **spleen** is slightly enlarged but is soft and diffluent, so that attention is not usually drawn to it clinically, there is hyperplasia of the lymphatic tissue

Similarly, there is hyperplasia of the **lymph nodes** in other parts of the body, particularly of the abdominal glands. The **bone marrow** shows leucoblastic hyperplasia with erythroblastic depression. There may be [illegible] ie stomach and intes [illegible] Cellular infiltration [illegible], and leptospiræ are [illegible]

Blood picture—There is usually a leucocytosis of 10 000 per c mm, a polymorphonuclear percentage of 80 to 85 with a leftward shift in the Arneth count, and a progressive anæmia, the indirect van den Bergh reaction

is usually positive even in an-icteric cases and in the cases with jaundice it is biphasic and may reach 60 units of bilirubin

Urine —There is usually a heavy cloud of albumin and often traces of blood, occasionally, hæmaturia may reach macroscopic proportions There is sometimes a decrease in the urea excretion, and later, after a period of anuria, there will often be a temporary increase Later, in the jaundiced cases, bile will appear

SYMPTOMATOLOGY

The attacks vary very considerably in intensity and from serological

The three pathological phases of the disease the leptospiræmic, the hepatic and the renal may not be clearly defined clinically Liver damage becomes evident from the fourth or fifth day and the renal only in the severest cases about the tenth day

The incubation period is from four to twelve days and the onset is usually sudden The fever mounts rapidly to reach 102°F or 103°F on the fourth day, continuing as a high remittent fever for a few days and then falling by lysis, the whole attack lasting about 10 days A febrile relapse after about three or four days of freedom from fever is not uncommon In severe and complicated cases the fever may last much longer, and tends to occur in a series of relapses

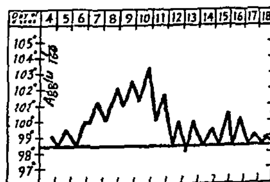


Figure 67 Temperature chart in Weil's disease

The pulse is rapid at first but often slows

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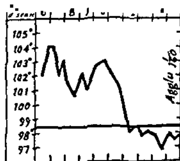


Figure 68 Case showing an early fall of temperature

is thickly coated and there is usually ... onset with

d

hæmorrhages from other mucous ... s may occur Rashes are not constant, a petechial rash may appear from the third to the fifth day, and a morbilliform rash from the fifth to the twelfth day in very severe cases the rash is hæmorrhagic

Anuria is not uncommon, and, even when some urine is being excreted, there is evidence of nitrogen retention

The hair tends to fall out, and, in milder forms of this infection, this is sometimes the first observation of the patient

The liver is usually palpable and the spleen occasionally so, the former is nearly always tender

Complications —The most important complications are bronchitis and broncho pneumonia, this is particularly true in cold countries

Iritis and irido-cyclitis have been described in some countries

Relapses —In about 30 per cent of febrile cases, there is a relapse of the fever at the end of the third, or early in the fourth, week This recurrence of fever is not accompanied by any reappearance of the leptospiræ in the blood, and is therefore not a true relapse comparable with that which occurs in certain other spirochætal diseases In this second bout, the fever does not usually rise much above 100°F, the temperature is usually irregular for a few days, and then falls again to normal

DIAGNOSIS

The diagnosis of Weil's disease, with any degree of certainty, on clinical grounds alone, is not easy, especially in cases in which there is no jaundice Demonstration of the causal organism in the blood or urine is the surest method of confirming the diagnosis but strong presumptive evidence may be obtained from the agglutination test

Leptospiræ are present in the **blood** of patients during the first week of illness, and can be isolated readily even as late as the ninth day **Microscopic examination** of the blood either by means of stained films or by dark-ground illumination is of little practical use as the leptospiræ are scanty and therefore very difficult to find by this means

Cultural examination gives fairly satisfactory results Vervoort's medium is the best to use, into 10 c cm of Vervoort's medium 1 c cm of blood is inoculated and the medium is incubated for at least one week either at room temperature or at 28° to 30°C In 60 to 80 per cent of cases examined within the first week, positive results are obtained

Animal inoculation is perhaps the most reliable method of diagnosis Three to five cubic centimetres of blood are injected intra-peritoneally into young guinea-pigs weighing about 250 grammes and their peritoneal fluid examined for leptospiræ by dark ground illumination from the seventh day onwards If the animal dies, a post-mortem examination is done, and sections of the liver and kidney are stained by Levaditi's method and examined for leptospiræ

The urine of patients may also show leptospiræ, they appear in the urine from about the tenth day of the illness, and may continue to be excreted for two months Repeated examinations are however necessary
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urine

Serological methods for the diagnosis of Weil's disease have also been developed The patient's serum and a weak formalinized culture of

leptospiræ are used, agglutinins begin to appear in the blood about the sixth day of illness, and are present for years after recovery Positive results in dilutions as high as 1 in 10,000 are common, and occasionally the titre rises to 1 in 1,000,000, but an agglutination of 1 in 100 is considered specific by some workers Such a low titre might indicate past infection, and, as in the Widal test, more attention should be paid to a rising titre As there are several serological strains of leptospiræ, the serum should be put up with all the strains that are available In some cases the urine also gives a positive agglutination test up to 1 in 250 dilution

Recently, Brown (1939) has described an *adhesion test* for the diagnosis of Weil's disease The patient's serum is mixed with a young culture of leptospiræ, a living culture of some motile bacillus, and fresh serum from a guinea-pig, the mixture is incubated at 37°C for half an hour It is then examined under dark-ground illumination A positive result is indicated by the motile bacilli adhering to the leptospiræ

DIFFERENTIAL DIAGNOSIS

In severe cases, the clinical picture will suggest yellow fever, in less severe cases 'bilious remittent' malarial fever or relapsing fever, in the last two, blood examination will clinch the diagnosis In cases in which jaundice is prominent, catarrhal jaundice will have to be excluded, but the fever will be lower and the prostration less in the latter case Severe hæmaturia may simulate the hæmoglobinuria of blackwater fever, but careful investigation will distinguish them Mild cases may suggest dengue, or sand-fly fever but the leucopenia which is the rule in these conditions, as well as the shorter duration of the fever, should help to distinguish them

PREVENTION

Successful control and prevention of Weil's disease depends upon—(a) the destruction of rats, (b) the disinfection of infected water and soil, (c) the protection of persons who are exposed to infection, and, in some circumstances (d) the diagnosis and treatment of cases and disinfection of their urine

(a) *The destruction of rats*—As rats are the main source of infection, war against rats is of the greatest importance Food stores and supplies should be protected by rat-proofing Attempts should be made to trap or poison rats and reduce their numbers

(b) *The disinfection of infected water and soil*—Contaminated water should not be used for bathing, washing, or drinking Infected water and soil should be disinfected, the latter by the use of calcium cyanamide, *this* is a fertilizer and is of special value in damp and water-logged agricultural areas About 168 lb of calcium cyanamide are required for one acre of soil For the disinfection of water in paddy fields, 44 lb of the fertilizer should be used per acre for each inch of depth of water Leptospiræ generally thrive in alkaline soils Acidifying the soil also helps to destroy the organisms Wherever possible, drainage of the soil should be effected

(c) *The protection of persons who are exposed to infection*—People [illegible] boots to

clean soap and water Persons with achlorhydria should be particularly

careful Cuts and abrasions received by workers should be promptly disinfected

In population groups under special risk vaccination should be con[illegible] as there are a number of serological strains of leptospira, the [illegible] tion of the vaccine, in order to [illegible] consist of 50 to 75 millions of [illegible] culations should be given at an [illegible] us vaccine has helped consider [illegible] e in Japan The protection is however apparently short lived and re-vaccination should be carried out at regular intervals of certainly not less than a year

(*d*) *The diagnosis and treatment of cases and disinfection of their urine*—Cases should be diagnosed early and admitted into hospital, if possible Their urine should be disinfected Convalescents should be detained until their urine is free from leptospiræ

Convalescents may be re employed as labourers about two months after recovery It is advantageous to employ them as they will be immune to infection

TREATMENT

The only specific treatment that has been effective is specific antiserum, either horse serum which has now been prepared on a commercial scale or convalescent serum An initial injection of 60 c cm of horse serum in a pint of saline should be given intravenously, with the usual precautions against anaphylactic shock this should be repeated next day, and each day, as long as it is indicated by the patient's condition A polyvalent serum, or better still one pr pared from all local strains should be used Of convalescent serum about 30 c cm is usually given and this is also repeated if necessary

Arsphenamine has no specific action in this infection

A pint of 5 per cent glucose in pyrogen free water and 5 units of insulin should be given as long as there is evidence of toxæmia In less severe cases isotonic rectal saline with 4 grains of calcium chloride to the pint is useful

Otherwise the treatment is symptomatic and must be indicated by the complications that arise The patient should be confined strictly to bed until some days after the temperature has fallen to normal and he should be kept on a fluid diet glucose albumen water and lime whey at first then milk and the diet should be increased very slowly during con valescence (*See* note on p 308 regarding high protein diet)

PROGNOSIS

The mortality from the disease is very variable and ranges from 2 to 50 per cent Death seldom occurs in the an icteric cases but in the writer's experience the death rate even under hospital conditions in cases with well developed jaundice is as high as 50 per cent

Age is an important factor in mild epidemics the deaths are often only amongst persons over 50 years of age The following is the percentage case mortality recorded in different countries in Japan 32 to 48 per cent, in Malaya 30 per cent in India 18 to 40 per cent in Scotland 25 per cent, in Germany 13 per cent in London 4 to 6 per cent in Belgium 4 to 6 per cent and in Italy 2 per cent These figures are based on clinically diagnosed cases and the higher figures probably exclude the mild an-icteric cases

SEVEN-DAY FEVER OF JAPAN

Introduction.—This is one of the milder forms of leptospiral infection the syndrome has been recognized in Japan for many years, and is known by the names *nanukayami* or *sakusku* fever Autumn fever is probably a variant of the same infection It was distinguished from dengue and shown to be caused by a leptospira (*Leptospira hebdomadis*) by Ido, Ito and Wani in 1918

There are many recognized strains of *L icterohæmorrhagiæ* which differ from one another antigenically but are apparently similar in their pathogenicity, at least, up to the present little correlation between particular strains and degrees of pathogenicity has been demonstrated The obviously low pathogenicity of *L hebdomadis* constitutes a difference which at present seems to warrant special differentiation, but nevertheless in time, intermediate strains may be encountered, and it may then be necessary to consider *L hebdomadis* as simply one strain of *L icterohæmorrhagiæ*, in such circumstances, seven day fever will have to be looked upon as a mild form of Weil's disease, which from a clinical standpoint it might well be

Autumn fever, pseudo dengue, and certain other short fevers of Java and Sumatra will also probably fall into line

Epidemiology.—It is a sporadic infection common in certain rural districts of Japan mainly affecting field workers

ÆTIOLOGY

The causal organism, *Leptospira hebdomadis*, is morphologically identical with *L icterohæmorrhagiæ* but antigenically it is quite distinct In guinea-pigs, it causes a febrile disease which is sometimes fatal, but it produces jaundice in only about 17 per cent of animals infected, *cf* *L icterohæmorrhagiæ* which is almost always fatal and causes severe jaundice in 100 per cent of animals

Transmission.—The reservoir of infection is the short eared field mouse *Microtus m* [illegible] in about 3 per cen [illegible] man by the same [illegible]

SYMPTOMATOLOGY

The onset of this disease is usually sudden, with high fever, headaches muscular pains loss of appetite, glandular enlargement, and occasionally a morbilliform rash *The fever sometimes runs a dengue-like course*, and in fact the disease was and probably still is, confused with dengue Otherwise, it is like a mild form of Weil's disease

Little is known of the pathology as the prognosis is uniformly good

The diagnosis is made in the same way as that of Weil's disease

The main points of distinction between this disease and dengue are the slow pulse and the leucopenia in the latter, the white cell count in seven-day fever is usually about 10,000 per c mm, and the increase is mainly in polymorphonuclears

The treatment is symptomatic, and the preventive measures that can be adopted are based on the knowledge of the reservoir of infection and common-sense application of this knowledge

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THE TYPHUS FEVERS

MURINE TYPHUS

ROCKY MOUNTAIN SPOTTED FEVER

TSUTSUGAMUSHI

'Q' FEVER

TYPHUS FEVER IN INDIA

THE TYPHUS FEVERS

Definition—The typhus fevers are a group of febrile diseases of varying severity caused by micro organisms of the genus *Rickettsia* and transmitted to man mainly if not entirely by the agency of insects

Introduction—In view of the fact that all the diseases hitherto recognized clinically as typhus have been shown to be rickettsial in origin *and that all diseases that are known to be caused by rickettsiæ have*

modify this nomenclature Som
there were 27 different names ap
the necessity for clarification and classification since he wrote this the
number has been adde
fication which has fo
From the point of view
between the epidemic

There are many
is not expedient nor would it be possible in the space at his disposal to discuss all these the writer proposes to describe only certain clear cut types that have appeared in countries outside India and then to discuss the disease as we see it in India

Historical—Typhus fever was distinguished from typhoid fever only about a century ago both by Stille (1838) and Gerhard (1837) though there are many earlier historical references to epidemics that were almost certainly typhus It

was always recognized as a very infectious disease, but the manner in which it spread from man to
Nicolle and Conseil
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(Wolbach 1919, 1
adequate description
to the causal or
organisms of the same group, which he called *Dermacentroxenus rickettsi* as the cause of Rocky Mountain spotted fever Japanese river fever, or tsutsugamushi disease, which had long been recognized clinically and known to be transmitted by mites was shown to be caused by a rickettsia which Sellards (1923) described and called *R orientalis*, the mild sporadic form of typhus that Brill (1898) described in New York, the slightly more severe but still mild sporadic form that occurred in Mexico and South-East United States (Maxcy, 1926), and 'trench fever' that occurred on both sides of the western front in the last war, were also shown to be rickettsial in origin, in 1925, the endemic typhus fevers of Malaya were linked up with this group of diseases by Fletcher and Lesslar, and the position was clarified by Lewthwaite and his collaborators (Lewthwaite and Savoor, 1940) In 1937 Burnet and Freeman showed that Australian 'Q' fever (Derrick, 1937) was caused by a rickettsia

Wilson (1909) reported the isolation from the stools of typhus patients of proteus-like organisms that were agglutinated by the patients sera and later Weil and Felix (1916) separated the special strain of proteus that gave a very high agglutination titre with the serum of patients suffering from epidemic typhus thereby introducing the test now usually known as the Weil Felix or the Wilson-Weil Felix test, which appears to be positive in most of the typhus fevers and is a further means of identifying them

In 1917 Megaw drew attention to the existence of endemic typhus in India, and suggested the tick as a transmitter

Thus during the last thirty years a number of diseases which occur in many different parts of the world have little in common epidemiologically, and are clinically often very dissimilar have been linked up and shown to be caused by some species of the genus *Rickettsia* It has only been possible here to outline the story and to mention a very few of the workers involved some of whom including both Ricketts and von Prowazek lost their lives during their investigations as the result of laboratory infections

Classification —Since Megaw suggested his classification according to the vector, a considerable advance has been made in our knowledge of the antigenic relations of the various rickettsiæ that infect man On an immunological basis, there are four main groups of typhus fever (*a*) classical typhus (with which endemic typhus is closely related), (*b*) Rocky Mountain spotted fever (*c*) tsutsugamushi, and (*d*) trench fever

The classification that has been adopted here is modelled on Megaw's original classification which has been modified to take into account recent

pod, and enzootic, that is (in this instance) from rodent to rodent This provisional classification is shown in table IV which also gives some of the outstanding clinical and other features of these diseases

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Further reference is made to these below



Pinkerton 1944

THE RICKETTSIÆ

These are a group of micro-organisms that fall between the bacteria and the filtrable viruses, not or
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ary scale and have become obligatory parasites, their enzyme systems have degenerated so far that they are unable to sustain saprophytic existence

The rickettsiæ* can be divided into several groups according to the distance they have descended in the evolutionary scale

(i) Non-pathogenic (to mammals) extra-cellular and intra-cellular rickettsiæ, a large number have been isolated from a variety of insects

(ii) Potentially pathogenic extra-cellular rickettsiæ—*e g R quintana* of trench fever

(iii) Pathogenic intra-cellular rickettsiæ that will also live extra cellularly under certain conditions, *e g R burneti* of Q fever

(iv) Pathogenic rickettsiæ that are obligatory intra-cellular parasites, these are sub-divided into two groups —

(a) the intracytoplasmic, *e g R prowazeki* and *R orientalis* of epidemic typhus and tsutsugamushi respectively

(b) the intranuclear, *e g R rickettsi (Dermacentroxenus rickettsi)* of Rocky Mountain spotted fever, these are also present in the cell cytoplasm

* Rickettsiaceæ (Wolbach, 1940) has been suggested as the family name for this group of organisms, but it would perhaps be more appropriate if a super family Rickettsoidea with families, say, Wolbachaceæ for the non-pathogenic and potentially extra-cellular organisms and Rickettsiaceæ for the obligatory intra cellular species of the last group, were created

TABLE IV FEVERS OF THE TYPHUS GROUP

Primary cycle	Epidemic	Enarthropodic	Enzootic			
Epidemiological classification	Communicated from man to man Associated with famine, filth and overcrowding	Diseases of special circumstances	Sporadic place-diseases communicated from natural reservoirs to man by various arthropods Mostly diseases of the open country			
Vector classification	Louse-typhus		Tick typhus		Flea-typhus	Mite-typhus
Names and synonyms	Classical type typhus fever, typhus exanthematicus	Trench fever Weigl's disease	Rocky Mountain spotted fever, western variety	Fievre boutonneuse tick bite fever	Murine endemic, urban or ship typhus	Tsutsugamushi Japanese river fever scrub or tropical typhus Sumatra mite fever
Distribution	Cosmopolitan Less common in the tropics	War conditions Laboratory infection	Rocky Mountain States U S A	Europe South America Africa Asia	Many localities all over the world	Oriental tropical and sub-tropical countries
Virus	*Rickettsia prowazeki*	*R quintana* *R weigli*	*R rickettsi*	*R conori*	*R muricola*	*R orientalis*
Vectors	Human lice (*Pediculus humanus*)	Human lice	*Dermacentor andersoni*	*Rhipicephalus sanguineus*	Fleas (especially *Xenopsylla cheopis*)	Mites (*Trombicula akamushi* and *T deliensis*)
Reservoirs of infection	Man	Lice	*Dermacentor andersoni* (no animal reservoir identified)	Rodents of the wilds possibly dogs and other domestic animals,	Rats and mice	Rats and mice
Serum agglutination response to OX19	+++	?	+	+	+++	— to ±
OX2	+		+	++	+	—
OXK	—		+	—	—	++ to +++
Rash	Macular or papular often faint Rare on palms, soles and face	Pink macules or papules	Maculo papular common on palms soles and face		As in louse type but often faint or absent	Macular or papular often on face rare on palms and soles
Local sore, lymphangitis and lymphadenitis	Nil	Nil	Nil	Common	Nil	Almost constant in Japanese mite-typhus often absent in other mite-typhuses
Mortality per cent	5 to 50	Very low	High 10 to 80	Low about 2	0 to 4	[illegible]

CLASSICAL, EPIDEMIC OR LOUSE-BORNE TYPHUS

Definition—Classical typhus is a severe febrile epidemic disease with a sudden onset, lasting 10 to 15 days and ending in rapid lysis accompanied by a rash that appears from the third to the fifth day, and caused by *Rickettsia prowazeki* which is carried from man to man by lice

EPIDEMIOLOGY

Geographical distribution—This disease has, or rather has had, a world-wide distribution It is certainly not 'tropical', though it might be considered *exotique*, it is actually much less common in tropical than in temperate countries

Recent epidemics have occurred in Russia, Poland the Balkans Ireland and Spain in Europe, in North Africa, in Asia Minor, Transcaspia Siberia and China, and in Colombia, Ecuador, Peru and Chile

Epidemic features—It is essentially an epidemic disease, and its incidence is clearly explainable on the basis of its mode of transmission It occurs in the less civilized countries in Europe where the sense of personal cleanliness of the individual is not highly developed, or where through circumstances his normal habits are interfered with, such as during wars, persecutions, and famines Its absence from many tropical countries can probably be explained by the small amount of clothing worn, which reduces the harbourage of the transmitting louse, and, in the case of India, on the cleanliness of the personal habits of the majority of the population

In addition to the transmission factor, the lowering of the resistance of the population by hardships and privations is probably important In such circumstances the natural [illegible] ered, so that the individual not only be [illegible] ntibody formation is poor and the viru [illegible] in the peripheral blood for a longer pe [illegible] circumstances, and therefore causes a [illegible]

Deaths from typhus in England and Wales which numbered about 4 000 annually in 1870 had fallen below 40 at the beginning of the century to disappear from the returns by 1920 The history of the disease in other sanitarily-advanced European countries has been similar

Season race and sex incidence—In its seasonal distribution typhus is more common in winter than in summer for the obvious reason that people tend to sleep herded together in their huts and wear more clothes in winter

All races appear to be equally susceptible to the disease but it tends to take a milder form in the races habituated to it (Napier, 1919)

The sexes are equally susceptible, the disease is usually milder in children

ÆTIOLOGY

The virus—The causal organism is *Rickettsia prowazeki*, the type species of the genus *Rickettsia* The rickettsiæ are granule-like bodies, more or less pleomorphic, with a diameter of less than half a micron, staining badly with aniline dyes, but well (purplish) with Giemsa's stain, they show a tendency to bi-polar staining In their behaviour they fall between the filtrable viruses and the bacteria, they do not grow on ordinary

laboratory media, but can be grown in tissue culture medium, or on the yolk sac of the developing chick embryo, which is the method used in preparing vaccines They are held up by fine filters, while they pass through coarse ones, as do small bacteria

These rickettsiæ are found in the cytoplasm of the endothelial cells of the blood vessel of their mammalian hosts, in the cells of the gut lining of lice, an intra-cellular position characterizes the pathogenic rickettsiæ and distinguishes them from the non-pathogenic varieties that are also found in certain arthropods In the blood stream the rickettsia tends to adhere to the red cells and platelets

Transmission—The virus circulates in the peripheral blood during the febrile period and defervescence The louse, *Pediculus humanus*, becomes infected by sucking the blood of its host, which is exclusively man, the rickettsiæ invade the endothelial lining of the gut of the louse, here they multiply, the cells eventually burst into the lumen of the gut, and the rickettsial bodies are passed out with the fæces, the cycle within the louse takes at least three days, usually longer, after which the louse is infective and remains so for the rest of its life The normal life span of the louse is about 14 days, but survival up to 45 days has been reported, the infection, however, tends to kill them The rickettsiæ survive in the dried fæces of lice up to 60 days, and the fæces are probably the main source of infection of man and the sole source of infection of the next generation of lice The extreme infectiousness of typhus depends on the fact that the dried fæces of lice may be blown about in the air of the sick-room or laboratory Man is infected by scratching the fæces into his skin, by contamination of his mucous membranes, or *via* the respiratory tract It is doubtful if gastro-intestinal infection takes place, and it is known that infection is not transmitted by the bite of the louse The cycle is thus man—louse—man The louse is an essential link and so probably is man, for *Pediculus humanus* feeds exclusively on human blood, and, though the infection may be transmitted to the next generation of lice by contamination, there is no hereditary transmission and, as the infection is fatal to the louse no louse-to-louse cycle would survive any length of time

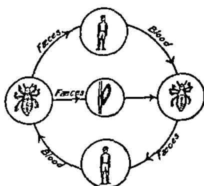


Figure 69 Transmission cycle in epidemic typhus

The possible modes of dissemination of infection are by (*a*) migration of infected lice, (*b*) by contact contamination with the infected fæces of lice, and (*c*) by air-borne infection from dried fæces of lice The former two have long been recognized and explain the rapid spreading of the disease when louse infected people are

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Immunity —The immunity produced by an attack is not complete, and second and even third attacks have been reported The comparatively mild form that the disease sometimes takes in communities where it is common can probably be accounted for by the previous attacks that these people have suffered, especially during childhood when the attacks are often very mild and might not be recognized as typhus

Passive immunity can be conveyed by the injection of the sera of convalescents, but as a practical means of protection this method is of little or no value

Active immunity can be produced by the inoculation of dead rickettsiæ (*vide infra*)

Cross immunity between classical typhus and the so-called Brill's disease has been shown to be complete, this is of course natural A considerable degree of cross immunity between classical and murine typhus (*e g* tabardillo of Mexico, *v i*) has been demonstrated, though this is not complete, but against the other forms of typhus there is little or no cross immunity The immunity runs more or less parallel with the Weil-Felix reaction

PATHOLOGY

Morbid anatomy —There are few macroscopic changes The spleen is usually distinctly enlarged, on section it is dark red, soft and diffluent There is cloudy swelling of the liver and kidneys Waxy degeneration of the muscles has been noted There are petechial hæmorrhages in the serous and mucous membranes and in the pons and medulla, and occasionally more extensive hæmorrhages into the hollow viscera the serous cavities, and even into the ventricles

[illegible] ndothelial [illegible] ickettsiæ, [illegible] vascular [illegible] of polymorphonuclears The tubercular nodules that are thus produced in the organs and tissues are suggestive of miliary tuberculosis These changes take place in the skin and cause the characteristic rash, in the mucous and serous membranes and cause hæmorrhages in the various organs, and in the central nervous system, the neuroglia cells taking part in the reaction, and cause the mental symptoms

There are no very characteristic changes in the **blood picture** In severe cases, especially when the patients first come under observation and are suffering some dehydration, there will be polycythæmia, there is usually a leucocytosis of 12 000 to 15,000 per c mm and an absence of eosinophils

The **urine** shows the characteristics that are usually associated with high fever, and often some albumin but there are seldom casts or other evidence of nephritis

SYMPTOMATOLOGY

The **incubation period** is usually from 10 to 14 days, extreme instances of incubation periods of 4 and 24 days have been reported

After a day or two of prodromal symptoms, general malaise, loss of appetite, headache, and joint pains the onset is sudden with the fever rising to its peak, 104°F or higher, in 48 hours, occasionally with a rigor This is accompanied by pains in the loins and joints, severe headache,

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extended fingers and fibrillary twitchings of the face and the speech is hesitant slow and slurred Vomiting is common and constipation is a constant symptom The pulse is full and soft usually about 100 per minute and the blood pressure is low

Nervous symptoms develop early, the patient is drowsy and apathetic and during consciousness cerebration is slow as early as the fourth day (*cf* typhoid in which the mental symptoms develop much later) T T
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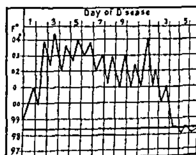


Figure 70 Temperature chart in a case of classical typhus (original)

The temperature as noted above rises rapidly to 104°F and remains as a high remittent temperature for 10 to 12 days at the end of this period it may show deep remissions and eventually it falls by rapid lysis The whole febrile period lasts from 12 to 17 days

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develop for a few days and they may become petechial or even hæmorrhagic
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time

Variations from the normal —The disease described by Brill in 1898 and shown by Anderson and Goldberger in 1912 to be a form of typhus has more recently been shown by Zinsser to be almost certainly a manifestation of late relapse of classical typhus for he found that in nearly every one of the 538 cases of this disease reported between 1910 and 1933 in New York the patients were emigres from Russia or other European countries where typhus is frequently epidemic This is a clinically mild type of typhus with no mortality usually with a modified rash which may be absent but the serum gives the typical agglutination against proteus X19

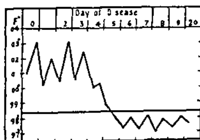


Figure 71 Temperature chart in a case of mild classical typhus which was diagnosed as broncho pneumonia but later shown by the Weil Felix reaction to be typhus (original)

Another modified form of the disease in which the clinical picture is

Complications —Broncho pneumonia is common, other complications are stomatitis, parotitis, and even noma, thrombosis followed by gangrene of the feet or toes, genitals, and ears characterize some epidemics Heart failure, preceded by a very low blood pressure and a slow pulse, is not an uncommon mode of death

DIAGNOSIS

In a typical case, the clinical diagnosis will present little difficulty, the points which differentiate typhus from typhoid are (i) sudden and rapid onset with the early development of severe symptoms, (ii) pains in the joints, limbs, and loins, and rigidity, (iii) the rash, (iv) the nervous symptoms and especially their earlier development (v) the leucocytosis, and (vi) the earlier and more rapid resolution

Of the laboratory methods, the **Weil-Felix reaction** is the most valuable This test is dependent on the probably accidental similarity of the antigenic structure of the specific rickettsia of typhus to that of a bacillus of the proteus group, X19, that was originally isolated from the urine of a typhus patient and found to be agglutinated in a high titre by his serum Though really a non specific test, this test is as specific as any 'specific' agglutination test in common use At the end of the first week, the patient's serum gives a positive result in a dilution of 1 in 100, and by the end of febrile period it may be as high as 1 in 5,000, agglutination persists for some weeks and probably for some years in a low titre, which may be raised by some other febrile attack It is not

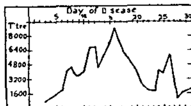


Figure 72 Graph based on the Weil Felix reactions on 85 samples of serum from definite cases of typhus taken at different periods during the disease (original)

More recently, an agglutination test with an emulsion of rickettsiæ has been developed but this test presents no advantages in this form of typhus

Of the more elaborate laboratory procedures guinea pig inoculation is the most useful, about 2 c cm of the patient's blood during the febrile period

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PREVENTION

In the face of an epidemic the first duty of the doctor is to protect his medical personnel, and incidentally himself The danger comes from louse infestation, contamination from squashed lice and lice-fæces, and from inhalation of dried lice-fæces A measure of special importance in this disease is the protection of medical personnel with masks, those dealing with dirty *dry* clothes should wear gas masks For other details of anti-louse measures, see above (p 231)

A great deal of attention has been paid to the subject of prophylactic *inoculation during the last quarter of a century* even when the prospects of producing a vaccine for wholesale inoculation seemed very remote on account of the obvious desirability of protecting medical personnel and laboratory workers Weigl (1924) produced the first successful vaccine from trituration of the intestines of infected lice, this method had very obviously a limited application The two methods that now promise success are those of Zinsser and his co-workers (1937) who have produced vaccine on a large scale by the combined agar tissue culture and a yolk sac culture methods, and of Durand and Sparrow (1940) who have produced a vaccine by inducing massive lung infections in mice by insufflation of rickettsiæ In animal experiments and for the protection of individual workers subjected to special risk, they have been successful but at the time of writing neither of these methods has been put to the practical test of the protection of large populations during epidemics, however it is probable that ample opportunities will soon arise in Europe if not elsewhere

We have certainly reached a stage where medical personnel might well be protected in this way, but at present in most circumstances the protection of a whole population by this means would be too expensive

TREATMENT

The treatment is almost entirely symptomatic Convalescent serum has been used but has not yet established any reputation The production of antiserum on a large scale has not yet been undertaken, but this may be possible now that the difficulty of getting rickettsial vaccine has been largely overcome

The patient must of course be kept strictly in bed throughout the fever and for some days after defervescence, and given a balanced diet, mainly fluid, with plenty of additional fluid to drink, the course of the disease is comparatively short, and it is not therefore so necessary to maintain a high calorie diet, as in the case of typhoid, but in milder cases it is advantageous to do so Hydrotherapy should be adopted to keep the temperature down, and strict attention should be paid to mouth hygiene and to the skin, particularly pressure points, which should be rubbed well with alcohol The bowels should be moved by a mild laxative given nightly and, if necessary, by an enema given every second day

In very dehydrated and toxic cases, intravenous saline has been used with success, in toxic cases, intravenous glucose (5 per cent) is also useful

A sedative will often be necessary, phenobarbitone should be tried first and then codeine, but, if neither is successful, it may be necessary to resort to morphia A lumbar puncture will sometimes relieve extreme restlessness Frequent small doses of brandy are very useful, and cardiac

stimulants may be necessary, camphor in ether or cardiazol is preferable to strychnine or digitalis Oxygen will often be useful

PROGNOSIS

The death rate is very variable and will depend on the conditions, for example, in time of famine and amongst half-starved and exhausted refugees it may be nearly 100 per cent, it will also vary from epidemic to epidemic but is seldom less than 10 per cent, in children the rate is low and in the aged high Death usually occurs about the 10th to 12th day

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TRENCH FEVER

Definition —Trench fever is a febrile disease of moderate severity which shows a tendency to relapse, it is caused by a rickettsial organism, *R quintana*, which is transmitted to man sporadically from the louse in which it is a saprophytic infection The disease appeared during the last war, mainly in the trenches on the western front, but also in Poland, Northern Italy and Macedonia, and has subsequently disappeared

Ætiology —The causal organism, *Rickettsia quintana*, is apparently a natural parasite of the louse, *Pediculus humanus*, and only infects man sporadically This rickettsia lives in the lumen of the gut of lice, and is never intra-cellular, its normal cycle is from louse to louse by contamination and only when he is subjected to intensive dosage with the virus does man become infected The infection is transmitted from the crushed bodies of lice or from their fæces, through an abrasion in the skin or *via* the conjunctiva Man is said to be infective to the louse from the third day of the disease, and to remain so well into convalescence but the early experimenters who demonstrated this do not seem to be

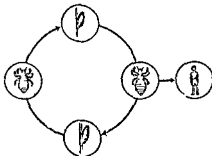


Figure 73 Suggested transmission cycle in trench fever

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The relation between *R quintana* (and *R weigli*, *vide infra*) and *R pediculi*, the natural rickettsia of the louse, is not clear These two rickettsiæ are indistinguishable, both morphologically and in their relation to the louse, as they are both extra-cellular and non-pathogenic in the louse, but the latter is normally non-pathogenic to man It seems possible that, in certain circumstances not yet determined, *R pediculi* becomes pathogenic to man As this disease has now disappeared, quite possibly only temporarily, it is impossible to study it, and the rickettsial organism that causes it, by modern methods

Weigl's disease, which is the name given to a localized laboratory outbreak of rickettsial infection, is almost certainly exactly the same disease, laboratory workers were infected through handling infected lice

Symptomatology —The incubation period is eight to ten days The onset is sudden, usually without prodromal symptoms, but occasionally there is headache, weakness, restlessness and diarrhœa In a few cases the onset is so sudden that the patient falls down, or becomes so giddy that he cannot walk, other symptoms are generalized pains vomiting and gastro-intestinal symptoms The temperature rises to 103°F, or so, and the fever continues for about three days, it then falls to normal for a day or two and again rises The periodicity varies between four and eight days There is usually conjunctival injection, a very dirty tongue, occasionally rose spots on the chest, that disappear on pressure, and a slightly enlarged hard spleen The blood shows a moderate leucocytosis The diagnosis is largely clinical and circumstantial, and by a process of exclusion At the present day, it would be unwise to make this diagnosis in the absence of a heavy infestation with rickettsia-infected lice

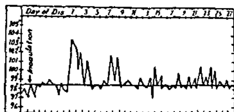


Figure 74 Temperature chart in trench fever (after Byam 1923)

Prevention and treatment —The louse is the essential factor and vigorous measures, indicated above, should be directed against this parasite Treatment is symptomatic

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MURINE TYPHUS

Definition —Murine typhus is a fever of the typhus group, of moderate severity, caused by *Rickettsia muricola* (*mooseri*) which is closely related to, if not identical with, *Rickettsia prowazeki*, and is transmitted to man by the rat flea, *Xenopsylla cheopis;* it occurs endemically in many tropical and sub-tropical countries

Synonyms associated diseases and geographical distribution —Included under this heading are *tabardillo*, or endemic typhus of Mexico and the south-eastern states of the U S A, ship typhus of Toulon (France), ... idemic typhus, and certain ... parts of the world, Syria,

ÆTIOLOGY

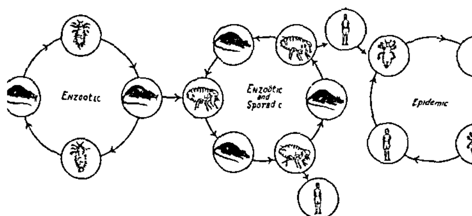
The causal organism is usually known as *Rickettsia muricola*, but is also referred to as *R mooseri* ... *R prowazeki*, and in its behaviour ... to it, in the flea, it is found in the gut, but it does not kill the insect ... is that *R muricola* produces scrotal swellings when inoculated intraperitoneally into guinea-pigs, but some doubt has been thrown on the stability of this differentiation by the observation that *R prowazeki* will acquire this characteristic if it is transmitted through a series of guinea-pigs

Transmission —The epidemiological investigations of Maxcy (1926), the later experimental work of Dyer *et al* (1931), and the co ordinating studies of Zinsser and his associates have led to a clearer understanding of this disease These studies have established the following facts The

main reservoir of infection is the rat (mice and other rodents also possibly act in this capacity), and the infection is passed from rat to rat by the rat louse *Polyplax spinulosus*. This louse is specific to the rat and does

the rat and man is very close (Compare the transmission of plague by the same rat flea in this case the rat dies, the infected fleas leave the dead rat to find new hosts, either rats or man, and a rapid dissemination of infection takes place, resulting in an epidemic)

Further, it has been shown that from man, the louse can acquire the



This demonstrates how the virus of typhus survives during the inter-epidemic periods, and seems to offer a very reasonable explanation for the apparent spontaneous generation of epidemic typhus

Zinsser has pointed out that the facts of the non pathogenicity of this rickettsia to the flea and its lethal effect in the human louse, suggest a much longer association with the former or in other words that endemic murine typhus was the older disease from which epidemic typhus originated

Epidemiology—The disease is sporadic It occurs where man lives in close association with rats in insanitary prisons, in crowded and insanitary bazars of tropical ports, on rat-infested ships, and in grain stores

In the endemic areas, the incidence of this disease may be such as to constitute an important public health problem, and even in the United States, the annual incidence is in the neighbourhood of 3 000, with a death rate of about 3 per cent.

In most of the endemic areas, it has no special seasonal incidence, but, in the colder countries where it occurs, it is a summer or autumn disease Individuals of all races and ages and both sexes seem to be equally susceptible

The relation of this disease to epidemic typhus has been suggested above When once the louse-man cycle has been established the disease takes on all the characters of classical typhus

Pathology.—This does not differ materially from that of classical typhus, but it has not been studied very thoroughly as deaths are comparatively rare

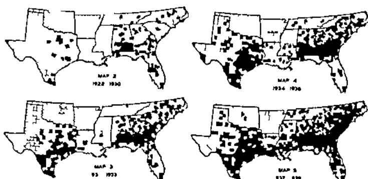


Figure 76 The extension of murine typhus in the southern states of the U S A (H E Meleney *Amer J Pub Health* **31**, *219*)

Symptomatology—The disease differs from classical typhus mainly in its intensity The **incubation** period is from 10 to 16 days, the **onset** is sudden and may be quite severe, but the severity is short-lived and the temperature drops to the 100°F line or so within a few days, the whole course is not usually more than 10 to 14 days The rash appears about the fifth day but is less intense The deaths are usually due to complications, *e g* broncho-pneumonia but occasionally an isolated case runs a severe course which may be indistinguishable from the classical disease on clinical grounds

The **diagnosis** is confirmed by a positive Weil-Felix reaction with the OX19 antigen (*vide infra*)

Immunity—It is on the immunological experiments that our knowledge of the close relationship of the murine and classical typhus depends In animals, previous infection with either virus produces a solid immunity against infection with the other, this lasts in some cases up to a year Whilst complement-fixation tests confirm the existence of this cross-immunity, quantitative experiments show that a positive result will occur in higher dilutions with the homologous than with the heterologous rickettsia Both rickettsial infections lead to the formation of agglutinins against proteus OX19 in animals and man

There is no cross-immunity against the other species of rickettsia

Prevention and treatment—It must be obvious that the preventive measures in this disease are on entirely different lines from those in epidemic typhus The main attack is on the rat, but it is obviously essential that the rat s fleas must also be destroyed, or they will migrate to other rats and possibly man, and will tend to disseminate the infection The methods to be adopted are numerous and varied, and will depend very largely on the circumstances (*vide* PLAGUE)

One could not advocate extensive and expensive measures for the sake of limiting this disease alone but rats carry so many other diseases and cause so much economic loss through their rapacious and destructive habits that any successful measures against these vermin must be a sound investment

The dangers of heavy louse infestation in areas of endemic typhus are worth stressing again here for even if other circumstances are necessary for the change over to the epidemic form to take place louse infestation is a *sine qua non*

Personal prophylaxis can be effected by inoculation with either the murine or the classical strain

Treatment is symptomatic, on the lines indicated above

ROCKY MOUNTAIN SPOTTED FEVER

Geographical distribution.—As the name suggests the disease was first recognized

Virginia North Carolina and Washington D C but a few cases have been reported from nearly every state in the union outside of New England Wisconsin and Michigan In Canada it has been reported from British Columbia and Alberta

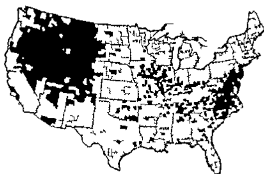


Figure 77 The distribution of Rocky Mountain Spotted Fever in 1941 (E C Faust 1944)

The typhus of Sao Paulo and Minas Geraes of Brazil and Tobia fever in Colombia are apparently the same disease Fièvre boutonneuse which occurs in France Portugal Roumania and North Africa Kenya typhus and the tick bite fever of southern Africa are closely allied diseases

ÆTIOLOGY

The virus.—The causal organism was originally named *Dermacentroxenus rickettsi* but was later shown to be a rickettsia and re-named *Rickettsia rickettsi* It has the morphological and tissue-cultural characters of the other intra-cellular rickettsiæ but is distinguished by its intra nuclear position It occurs in nature in the wood tick and

in other ticks Many wild rodents as well as laboratory animals can be infected and in the guinea pig it produces fever and the characteristic scrotol lesion (Neill Mooser reaction)

Transmission—The two principal transmitters are the wood tick *Dermacentor andersoni*, and the dog tick, *Dermacentor variabilis*, the former is the main transmitter in the mountain states and the latter in the eastern states In the southern states, *Amblyomma americanum* has also been found infected in nature and is probably a vector Many other ticks are potential vectors In Brazil, *Amblyomma cajennense* is the tick incriminated, and in France the dog tick *Rhipicephalus sanguineus*

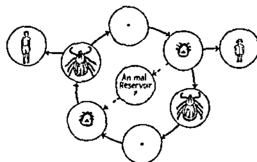


Figure 78 Transmission cycle in Rocky Mountain spotted fever (Western variety).

It is often stated as a definite fact that wild rodents and certain small carnivores, jack-rabbits, chipmunks, porcupines, weasels, etc, constitute a reservoir of infection Though none of these animals has been found infected in nature in the endemic areas, many are susceptible to the infection and it seems probable that they help to maintain this widespread sporadic infection It has however been pointed out that no reservoir is necessary, since the infection is transmitted to the progeny of the ticks in the case of the main vector, *Dermacentor andersoni*, through an infinite number of generations

The adult ticks bite man and transmit the disease to him, and the nymphs and larvæ will sometimes be found on children The percentage of ticks infected is comparatively small, in the enzootic areas this varies from place to place, and from year to year in the same place, but the general average is about 2 per cent, and it seldom rises above 10 per cent of a sample of ticks examined

In a starved tick the infection is dormant and it takes some time befo
and
that
starved infected tick has been fed on a susceptible animal for as long as three days, without transmitting the infection The infection is transmitted by the bite of the tick and by squashing infected ticks

Immunity—The immunity produced by an attack is not complete and many instances of second attacks have been reported There is no cross-immunity with other forms of typhus except those that have been recognized as closely allied diseases (*v s*) The serum agglutinates proteus OX19 and OX2, but in rabbits, the Rocky Mountain spotted fever strain will give rise to agglutinins against OX2, whereas the typhus strain will not Some immunity can be produced by inoculation with a vaccine

Epidemiology—The incidence is sporadic In the mountain states, it is to some extent an occupational infection, in that those engaged in hunting and trapping game and rodents, and in agricultural pursuits, are most

likely to be infected. Others that are frequently infected include prospectors and miners, highway construction workers, and tourists and picnickers. Thus, men are most frequently infected in these areas, but in the eastern states where the dog tick is the carrier, the tick is brought into the houses, and women and children are more frequently infected.

The intensity of the diseas
tricts, in the Bitter Root valley
rate has been as high as 80 per
40 per cent in the mountain di
eastern states, where *Dermacentor variabilis* is the transmitter, it is much lower, and the average death rate is probably less than 25 per cent. The lower death rate in the eastern states is certainly in part, and possibly entirely, due to the lower age-incidence in these states (Topping, 1943). The severity varies from year to year in any one area.

Pathology.—The rickettsiæ invade the endothelial cells and also the muscular coat of the smaller blood vessels so that thrombo necrosis is the reaction rather than proliferative endarteritis. Of the macroscopic lesions extensive ecchymoses into the skin, mucous membranes, and serous cavities, enlargement of the spleen, meningeal congestion, broncho-pneumonia, and scrotal gangrene are common.

In the **blood** there are no characteristic changes; there is usually a moderate leucocytosis, but a leucopenia (granulopenia) is not uncommon. The **urine** is acid, *it is often reduced in amount, and retention may occur*. Some albumin may be present.

SYMPTOMATOLOGY

The **incubation period** is from three to twelve days, being shorter in the more severe infections; after a day or so of prodromal symptoms,

supra).

The **temperature** rises by rapid steps to a maximum between 103°F. and 106°F., according to the severity of the attack, in five or six days, it maintains its height for a few days often with deep remissions, and then begins to come down by lysis, taking three to four days in the eastern type and seven to eight in the more severe western type, the whole febrile period lasting from two to three weeks. Fatal hyperpyrexia with temperature above 108°F. sometimes occurs.

***The rash** usually appears from the second to the fourth day but may* be delayed to the fifth or even sixth, and is sometimes preceded by a subcuticular mottling of the skin. The typical rash is bright red, macular or maculo-papular, it appears first on the wrist and ankles, sometimes on the forehead or back, it spreads rapidly all over the body including the palms and soles. In severe cases it commences with small pin-head spots

that rapidly darken and eventually become hæmorrhagic and coalesce In the less severe cases the spots appear in a succession of crops at a few days interval The rash fades slowly leaving a brown sta n which is very photosensitive becoming red on exposure and sometimes pock marks

The **pulse** is full and bounding and often disproportionately slow in the mild cases but in the toxic cases it becomes very rapid and is often un countable

Convalescence is usually slow and it may take some months

The common **complications** are pneumonia phlebitis and hæmorrhages including cerebral rarely and less frequently iritis and acute nephritis

Sequelæ are not common but neuroses psychoses and insomnia deaf ness impaired vision anæmia and myocardial weakness have been reported

Diagnosis does not present any difficulties in a typical case but the temperature may suggest typhoid other conditions that will have to be considered are measles and other acute exanthemata secondary syphilis meningitis and purpura hæmorrhagica

Further evidence will be obtained from the Weil Felix reaction stand
OX2 at 1 in 320 or higher should be
omplement fixation test will confirm
tl e disease from the other rickettsial
hus and tsutsugamushi but not from
Sao Paulo and Tobia fever

Another laboratory test is the inoculation intraperitoneally into a guinea pig of 1 c cm of blood taken from the patient during the febrile stage In the severe types there is a characteristic scrotal swelling which may lead to gangrene but in milder types this may be fleeting or absent there is always some febrile reaction and often the guinea pig dies Death does not follow other rickettsial infections

Prevention and treatment—Personal prophylaxis includes protection against tick bites by means of suitable clothing for example riding breeches and boots women should wear similar clothes When there has been any chance of tick infection the lower limbs and body should be
touch
ezing it
or pure
means
infection may be obviated

In the districts where the dog tick is the carrier dogs should be washed in some insecticidal solution to prevent ticks adhering to them whenever they have been out hunting and the inadvisability of allowing them to come into the house at all is obvious Great care should be exer cised in removing ticks from dogs as several persons have infected them selves by this means

Vaccination has now been practised for a number of years and it has been shown that some considerable degree of protection is given However it is obvious that there is room for improvement in the vaccine for many inoculated persons have died as the result of infection with the virulent western strain This is probably largely a matter of dosage and with the improved technique of the last few years a better vaccine should be forthcoming Re vaccination each season is advisable

Prognosis —This has been discussed above The main factor is apparently age In children the death rate is low and in the elderly and middle aged it is always high

Treatment is symptomatic and does not differ from that of classical typhus No known drugs are of any value

ASSOCIATED DISEASES

Associated diseases include the **tick bite fever** of southern Africa the [illegible] which [illegible] s have [illegible] *phalus* [illegible] In the last named hereditary transmission for a number of generations has been proved The reservoir of infection if such exists is presumably a veldt rodent and cattle and dogs act as conveyors of ticks to the vicinity of man The infection is transmitted by the bite through an abrasion or via the conjunctiva in the latter case from contamination from a squashed tick Clinically it is usually a mild infection with a low death rate less than 1 per cent There may be an initial lesion of the *tache noire* type and there is usually a rash about the fifth day The fever lasts about 14 days and ends by rapid lysis In elderly patients femoral thrombosis appears to be a common complication pulmonary thrombosis has also been reported The Weil Felix reaction shows a late development—after the 10th day—and is positive with OX2 and OX19 antigen in moderately high titre the former being higher than the latter usually (*vide* Gear 1940)

Fievre boutonneuse (*v s*) which occurs in the south of France and along the north African coast is caused by *Rickettsia conori* which is probably identical with *R rickettsi* it is transmitted from the dog which may act as a reservoir of infection by the dog tick *Rhipicephalus sanguineus* it is a comparatively mild form of typhus with a low mortality (2 per cent) there is an initial lesion—the *tache noire*—which is similar to that of tsutsugamushi disease (*v i*) but antigenically the disease is more closely related to Rocky Mountain spotted fever The serum agglutinates proteus OX19 and OX2

In Sao Paulo typhus of Brazil the infection is transmitted by the tick *Amblyomma cajennense* possibly from a rodent reservoir It is a severe disease with a high mortality (70 per cent) and similar both clinically and antigenically to Rocky Mountain spotted fever

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TSUTSUGAMUSHI

[illegible] fever is a disease of [illegible] transmitted to man by [illegible] from field mice rats [illegible] al lesion and adenitis and it runs a severe course the serum of the patient agglutinates the proteus organism OXK

[illegible]

the pseudo-typhus of Sumatra are certainly the same dise
disease is also reported from Indo-China and the Philippine

ÆTIOLOGY

The virus —The causal organism is *Rickettsia oriental*
or *R tsutsugamushi*) This species is far more refractor
propagation than the other species of rickettsia Infecti
only with considerable difficulty in guinea-pigs, after lower
resistance, bu
mitted to r
ocular inj
monkeys an
dermal inoc
siderable r
latter it pr
ulcer, a
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against O

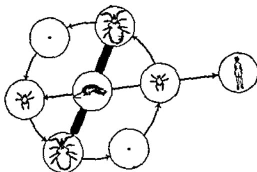


Figure 79 Transmission cycle in tsutsugamushi disease

Transm
tion is tra
in Japan
mushi, in
Trombicu
Queenslar
Lælaps australiensis The larval mites, which only t
become infected from field rodents, (*e g* in Japan
montebelli), transmit the infection to their offspring,
of the next generation pass it on to man by their
infection) The small mite, measuring only 0 25 m
to the naked eye, and being easily overlooked, rema
days The infection from this small insect is a ve
therefore causes a local lesion, it is suggested that
lesion in certain cases indicates that sometimes
proboscis reaches the deeper layers of the skin, is

Immunity – Cross-protection tests with gu
monkeys show complete reciprocal cross immunity
and the Japanese type of tsutsugamushi, but not
typhuses The specific proteus is the OXK

Epidemiology —The disease is an endemic
presence of the reservoir of infection and the trans
almost exclusively amongst farmers and other field
wardens and hunters In Malaya, practically
been in the habit of walking through the long *lala*
workers on oil-palm estates, especially those who
of the trees where rats forage for food

The disease occurs mainly amongst adult
occupational associations, but probably for no o
amongst children doing similar work, persons o
ally susceptible but the initial lesion and th
l skin

hæmorrhages in two cases, 11 enlarged spleens of which eight were diffluent, enlarged lymphatic glands in 10, and petechial hæmorrhages in the heart in four, in the pleura in 11, and in the kidneys in five cases

The blood shows a leucopenia or a normal leucocyte count, very rarely a slight leucocytosis There is an actual or relative increase of lymphocytes, a slight increase of monocytes a granulopenia and usually complete absence of eosinophils The *urine* shows traces of albumin, and the usual characters associated with fever

SYMPTOMATOLOGY

The incubation period in this infection varies over a wide range, from 5 to 21 days The onset is usually sudden, all symptoms developing within 24 hours, but occasionally there is a prodromal period lasting a few days with a slight headache and malaise the first definite symptoms

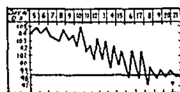
develop

The initial lesion that occurs at the site of the bite was at one time diagnosis of this form of typhus, but



Figure 80 Temperature chart in Malayan XK typhus with an initial lesion (*see* plate X figure 4)

and Sumatra it is apparently very common, in Malaya it is rarely found The lesion is at first macular then papular and eventually a necrotic centre develops which separates and leaves a punched out ulcer It is very probable that in a number of cases it does not go beyond the macular or papular stages and heals before the main symptoms develop That it is noticeably more common in fair-skinned individuals adds support to this suggestion



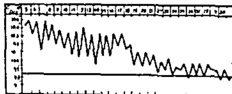


Figure 81 Temperature charts in tsutsugamushi disease (after Nagayo 1923)

The typical lesion at the time of onset of general symptoms is a depressed necrotic eschar about 5 mm in diameter with a well-defined areola of about the same breadth

The fever usually rises rapidly to 101 or *102°F*, and then after a further few days reaches its maximum of 104° or higher, and is maintained at this level with deep morning remissions of two or three degrees, until the end of the second week, when it falls by rapid lysis, after this there may be one or two final kicks in the temperature chart up to 100° or 101°, during the next day or so, before the fever finally subsides In the Japanese type, the lysis may take several days and a low fever may continue for another week As in other typhuses, the height of the fever is *not a guide to the severity of the infection*

The pulse rate is usually increased with the temperature, though a few cases in which it remained slow have been reported, in convalescence there may be bradycardia

The lymphatic glands, es

and tender

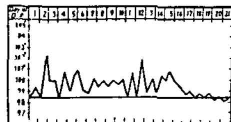


Figure 82 Temperature chart of a case of scrub typhus in Malaya (Anigstein 1933)

Nervous symptoms are usually pronounced, and develop as the temperature rises, there are fine tremors of the lips and tongue, and twitchings of the face muscles, the patient is dull and apathetic during the day and often delirious at night, insomnia is common, he may become stuporous and eventually pass into coma Another symptom is deafness, this is irregular but tends to develop throughout the disease

Complications—The only frequent complications are bronchitis and broncho-pneumonia

ial lesions or even of the remains of
nosis of this type of typhus though
teristic clinical feature, others are
with an increase in lymphocytes

The Weil-Felix reaction gives agglutination in high titre against proteus OXK, and a negligible agglutination with OX19 and OX2 The lowest titre that can be accepted as diagnostic is 1 in 250, but, as a few cases of leptosp ... OXK
proteus, di ... to
demonstrat ... may
be obtaine ... is
refractory ... g

If mice are inoculated intraperitoneally with the supernatant fluid from a blood clot ground up in saline they will die within 16 days and show abundant rickettsiæ in their peritoneal membrane

Prevention and treatment —The adoption of suitable clothing when in endemic areas and careful inspection of the body after removing the clothes are obvious measures for personal protection Prophylactic inoculation is being developed for this as well as for other typhuses In special circumstances rodent extermination may be advisable where the specific reservoir has been identified but such a measure should not be advocated lightly

Prognosis —The infection is less severe in children and very fatal in old people In Japan the death rate is given as 30 to 60 per cent and in Malaya as an average of 15 per cent

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Q FEVER

The most recent recruits to the typhus fevers are the so called Q fever first reported from Brisbane (Derrick 1937) and the American Q fever which takes the form of a pneumonitis these two diseases appear to be caused by antigenically identical rickettsiæ

The Australian disease is confined almost entirely to abattoir and dairy workers except that many laboratory infections have occurred

The Queensland bandicoot *Isoodon torosus* provides a reservoir of

[illegible] steps [illegible] this cycle of infection that still have to be confirmed especially with regard to the part played by *Ixodes holocyclus* but it would appear to be as shown graphically below —

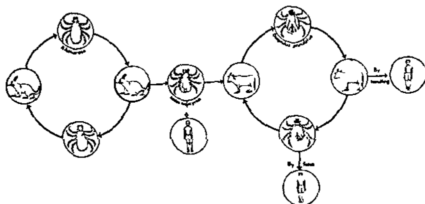


Figure 83 Probable transmission cycles in Australian Q fever

The causal organism *Rickettsia burneti* infects the endothelial cells lining the alimentary canals of the susceptible ticks. The rickettsiæ

multiply in these cells which eventually burst into the lumen of the ali mentary canal, and the rickettsiæ are passed out with the fæces

Infection may take place by the handling of the cattle harbouring infected ticks from the tick fæ epidemiological evidence that from the infected dust of the in casual visitors to abattoirs)

The infection is transmissible to guinea pigs monkeys and other domestic and laboratory animals but mice appear to be most susceptible and from their livers and spleens large numbers of rickettsiæ can be re covered with which agglutination tests can be carried out

Immunity develops in an infected person or animal and their serum will agglutinate the rickettsial emulsions There is cross immunity against *the rickettsia that causes American 'Q fever* but not against any *other* rickettsia *e g R rickettsi* or *R prowazeki* No agglutination occurs with any of the recognized proteus X strains

The clinical picture is that of a mild form of typhus with a low mortality in the typical case the onset is sudden the fever rises to as high as 104°F with deep remissions it lasts for about a week and then falls by crisis There is another form in which the fever runs a more chronic course other symptoms are intense persistent headache photo phobia and conjunctival congestion There is usually marked bradycardia There is no rash

The American form of Q fever has an interesting history in that it was an example of a disease in which the causal organism was *discovered* before the disease A rickettsia which was antigenically different from Mountain spotted fever the tick *Dermacentor* outbreak of pneumonitis being experimented with ith pneumonitis who had ks

In the case of the laboratory infections many persons of whom one died who had had no direct contact with the cultures or infected an mals were infected so that it seems probable that the infection was air borne *possibly spread by dust*

The causal organism of this American Q fever was called *Rickettsia diaporica* but it has been shown to be antigenically identical with *R burneti* which has precedence

The position of this disease *vis a vis* other typhuses is not yet clear ncluded in the provisional other features common isal organism though a siæ in its pathogenicity

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TYPHUS FEVER IN INDIA

A ent on was first drawn to this disease in India by typhus like fever that had occurred the clinical similarity between the nd he strongly suspected that the If the patient) The importance of

this observation will be realized if we remember that at this date no form of tropical typhus had been recognized as such, and little was known about any of the non epidemic typhuses Megaw later described other cases of typhus occurring in India, in which the patients had been bitten by unidentified ticks, in other cases, though there was no direct history of a tick bite, the possibility could not be excluded

Since this date, a number of cases of typhus and suspected typhus have been reported from various parts of India The most important publication on the subject is that of Boyd (1935) who collected data from 110 cases that had occurred in the army, or in persons associated with the

any of the previously recognized insect vectors were involved

ition has
ned with
blood of
isolation
vectors

Competent research workers have been engaged in these investigations and the inconclusive results that have been produced are due to the circumstances, mainly the extremely sporadic nature of the disease in this vast country, though the annual incidence probably runs into tens of thousands

n isolated from
rat fleas, and a
The monkeys
a reservoir of
bicula deliensis,
dilution of 1 in

50 in 32 per cent of instances and at a dilution of 1 in 25 in nearly all others, whereas the plains monkeys not so infested give a much lower grade of agglutination

The only possible view to take of the position is that in a vast country like India, with almost every possible climate represented it would be very surprising if there were only one type of typhus A more reasonable hypothesis is that each of the major groups is almost certainly represented our object should be to sort them out and attribute to each its special clinical picture, its vector, and its reservoir of infection so that they can be recognized and appropriate measures of prevention can be adopted rather than to stress their similarity—beyond the fact that they are typhus fevers—and to claim for them homogeneity

The fortunate accident of the close antigenic relationship of the different rickettsiæ to certain specific strains of proteus will serve us for the time

greater extent than they have been in the past, by investigators in India. Meanwhile, it is important that clinicians should make themselves familiar with the clinical pictures in the different types of typhus that occur in other countries, so that they will recognize them when they encounter similar diseases in India, and that bacteriologists should include the proteus group of organisms in their Widal tests, even when physicians do not ask for this test specifically.

Classification.—At the present date, Boyd's classification of the typhuses of India is the only one worth quoting; this classification has its strict limitation, as Boyd would be the first to admit, and it is to be hoped that it will soon be replaced by a more satisfactory one. Boyd's classification with certain important clinical and other data is given in the table below:—

TABLE V

Type		XK	X2	X19	
				Poona Ahmednagar	Bangalore
Geographical distribution		Northern, Eastern and Southern Commands except Poona Ahmednagar area and Madras District. Not reported from Western Command	Deccan District and Poona Independent Brigade Area only	Deccan District, C. P. and Poona Independent Brigade Area only	Southern Command except Poona Independent Brigade Area and Ahmednagar vicinity
Seasonal incidence maximum months		August and September	December	December	More or less evenly spread except February, March and April
Rash:— *Number of cases*	*British*	15/21	8/8	10/10	5/6
	Indian	1/14	5/6	6/6	1/21
Day of appearance	*British*	5th or 6th	3rd or 4th	3 d	4th to 10th
	Indian	7th			8th
Type		Flush, macules	Macules, papules, petechial	Macules, papules, petechial	Maculo-papular
Distribution		Trunk only	Generalized	Generalized	Trunk and limbs
Duration in days	*British*	7	18.4	25	4
	Indian		14.4	10.5	3
Staining		Nil	In some cases	In some cases	
Average duration of pyrexia in days		14.2	12.5	15.5	10.4
Average stay in hospital in days		31	27.5	29.5	24.6
Proteus agglutinins	XK	+++	±	±	±
	X2	−	+++	±	±
	X19	−	+	+ to ++	+++

Epide
tion with
in many
developed
time Many reports recently received have been of cases amongst town residents

able to attempt to correlate
are probably descriptions
ical descriptions are given
his case as follows —

The first symptoms were malaise and headache, which gradually increased until the fourth day The headache was referred to the orbits just above the eye-balls and from the fourth day it steadily subsided The only other symptoms were weakness and some pain and discomfort in the muscles of the back which caused disturbance of sleep for two or three nights

On the fifth day a diffuse macular erythema was noticed all over the body including the palms and soles and the face In the neighbourhood of each spot there was at first swelling and tenderness of the skin so that flexion of the fingers was painful

In a day or two the eruption became more pronounced the colour changing to brownish red about the eighth day the spots had a distinct tendency to be petechial and by this time the swelling and tenderness had disappeared The eruption faded rapidly with the fall of the temperature but a brown staining at the site of the spots was visible for about five weeks afterwards

On the front of the right thigh where the spots were readily observed and

There were no symptoms referable to the respiratory or nervous system and the patient took a keen interest in the progress of his case Convalescence was rapid he got up from bed on the day on which the temperature fell to normal and ten days later was in his usual good health

The leucocyte count on the tenth day was 15 400 per c.mm

Boyd (1935) described the clinical picture of the most important group, XK, in his classification, as follows —

Severe headache was a very constant and early symptom The face was usually flushed and the conjunctivæ somewhat injected Rigors and sweats were common in the early stages and toxæmia with its accompanying symptoms of lassitude and drowsiness was of varying severity Severe pains in the joints or 'all over the body' occurred in several cases

The rash was by no means a constant feature being present in only 15 of the 21 British cases and in only 1 of the 14 Indian cases It usually appeared on the fifth or sixth day but was recorded as early as the first and as late as the eighth day of illness

The rash appears on the fifth day of the disease A flush may be present on the fourth day This may be demonstrated on an apparently normal skin by the pressure of the hand The paler impression produced by the palm and fingers persists on the skin The rash is that of true typhus though the lenticular papules have not been observed It is a dusky erythema with scattered irregular blotchy underlying macules purple in colour The macules persist on pressure in some degree, while the flush fades leaving the skin very pale by contrast
r raised but cannot be felt The
ic areas and over the lower ribs
ribution of the flush is wider, it is
n of the upper part of the front
areas It is particularly well seen
The rash has been seen on the
not affected It is not very striking in appearance and may not be noticed It fades gradually the flush disappearing earlier than the macules As a rule it is no longer visible at the termination of the pyrexia

It is worthy of note that in no case of this series did the rash become papular or petechial nor, with one exception did the macules extend beyond the trunk. The macules were found chiefly on the abdomen and thorax, the face and neck and extremities were unaffected

The inconspicuous nature of the rash no doubt affords the explanation of its apparent rarity in Indian patients as it is presumably obscured by the pigmented skin

The average duration of the rash, calculated from figures given in thirteen cases, was seven days There was however, difficulty in determining the exact time when it could be said to have disappeared

Complications and sequelæ were by no means uncommon Nine cases showed pulmonary symptoms, 5 developing bronchitis, 2 pneumonic symptoms and 2 pleurisy Three cases developed acute mental symptoms, and 2 others varying degrees of transient paralysis

The average duration of fever (33 cases) was 14.2 days During the pyrexial period the pulse rate was relatively slow, resembling in this respect the pulse in fevers of the enteric group

Recovery was by lysis and in some cases by crisis In uncomplicated cases all other symptoms disappeared and convalescence was rapid as soon as the fever subsided

The average stay in hospital (35 cases) was thirty one days

Recent observations—A few notes are added on three recent reports on outbreaks of Indian typhus fevers

Heilig and Naidu (1942) reported 14 cases in Indians in Mysore, from the city and surrounding country All the cases were sporadic, they occurred between August and February, and there were no indications regarding the transmitting agent The onset was sudden, but without rigor, with malaise, headache, photophobia, body aches and usually conjunctival suffusion No splenic enlargement was noted The temperature chart showed a moderately high remittent fever which lasted from 16 to 21 days and resolved by rapid lysis (*see* figure 84) The rash first appeared between the fifth and the tenth days, it started as a pinkish macular rash on the trunk and upper extremities, and it spread all over the body, and to the lower part of the face in a few cases The rash became maculo-papular, the pink colour changing to purplish, and then petechial, desquamation occurred during the fourth week, and, finally, it turned to brown and left a stain that persisted for months There was a distinct leucocytosis in most cases

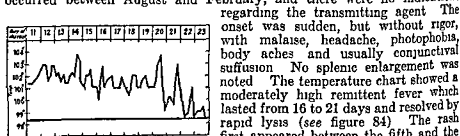


Figure 84 Temperature chart of a case of Indian endemic typhus

The diagnosis depended on the demonstration of rickettsiæ in the tunica vaginalis of guinea-pigs injected with the blood of some of the cases but in only one case was a Neill-Mooser reaction produced in the injected guinea-pig

The Weil-Felix reaction was positive with the OX2 antigen in most of the cases, though there was some co-agglutination with the other two antigens

PLATE IX

Fig 1—Rash in epidemic typhus (Army Medical Museum)

Fig 2—Rash in Rocky Mountain Spotted Fever (Army Medical Museum)

Fig 3—Primary ulcer in a case of Malayan scrub (XK) typhus (after Fletcher and Field, 1929)

Plate IX (Typhus)



Fig 1

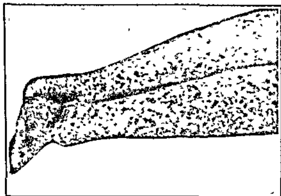


Fig 2



Fig 3



Fig 1—A case of Indian typhus (proteus agglutinations negative) 29th day of disease



Fig 2—Same as figure 1



Fig 3—Rash in Indian typhus (after Heilig and Naidu 1941)

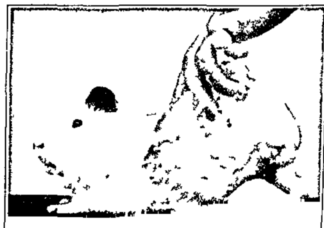


Fig 4—Neill Mooser reaction (after Heilig and Naidu 1941)

A second report was from a military hospital (personal communication from Lieut.-Colonel T A A Hunter, R A M C) The patients were eleven British soldiers, who had been in camp near Bombay during the month of November, the symptoms developed in one case 17 days after arrival at the camp, and in another 10 days after leaving it, so that if infection took place in the camp—an almost inevitable conclusion—the incubation period was between 10 and 17 days, but there was no history of tick bite in any case Eight cases occurred in one battalion

The onset and the course of the disease was very similar to that of the Mysore cases, but the symptoms were exceptionally mild, the fever was also of the same nature and lasted from 13 to 16 days The rash was also a marked feature in this series but developed within 24 hours of the onset of symptoms in every case and in two was the first evidence of the disease, it developed in the lower extremities first and spread rapidly all over the body except *the face* *This early development of the rash* constituted the only striking difference between the two series

The Weil-Felix was positive with the OX2 antigen in six cases, but in no case was a positive Neill-Mooser reaction produced in injected guinea-pigs

These two series have a number of features common with Boyd's X2 group (*see* table V), but the difference in the time of appearance of the rash is interesting There is no clue in either case to the transmission problem

A third outbreak occurred in Calcutta in the autumn of 1942 The patients were again British

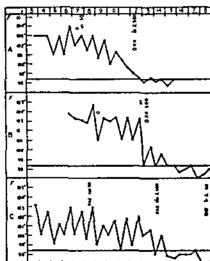


Figure 85 Temperature charts in three Calcutta cases of typhus

developed in nearly all of them The temperature charts were very like the classical typhus chart,

but in one case with OX2

patients was louse-infected

we know that the disease
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have the example of the
typhus has apparently

increased ten-fold and Rocky Mountain fever has spread from the western states to the east coast We must use the Weil-Felix test to help us to identify the disease, but we should be careful not to accept the indications of the test without clin cal s pport – th f
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OROYA FEVER, OR BARTONELLOSIS

very common secondary manifestation is the granulomatous eruption previously known as verruga peruana

Historical.—It is believed that the fatal disease which wrought havoc in Pizarro's army in the 16th century was Oroya fever

Medical attention was first drawn to it in 1870 when during the building of the railway to Oroya 7 000 deaths occurred amongst imported labour It was from this that the disease received its name which is a misnomer as it does not actually occur in Oroya

In 1885 Carrion a medical student inoculated himself from a verruga nodule and developed a fatal attack of Oroya fever From this time local physicians have assumed that the fever and the subsequent eruption were manifestations of the same disease The causal organism was identified by Barton in 1909 and his observations were confirmed by Strong and others in 1915

The ætiological identity of the two conditions was again questioned by the Harvard Commission in 1913 but Noguchi's cultural work re-established the claim for their identity and later Mayer Borchardt, and Kikuth (1927) produced both the local lesions and the severe febrile disease with anæmia, the latter after splenectomy, in monkeys by inoculation of material taken from a case of verruga peruana that arrived in Hamburg These observations were confirmed by the Harvard Commission of 1937, in this instance cultures were used for producing infections in monkeys

EPIDEMIOLOGY

Geographical distribution —It has a limited distribution in South America between 2°N and 13°S It occurs mainly in Peru, but recently indigenous cases have been reported from Bolivia, Ecuador and now Colombia The area in Colombia is in the basin of the Guaitara river, a fertile area with 100 000 inhabitants, the death rate from this disease in the first eight months of 1938 amounted to 1,800 persons

Other epidemiological features —The disease is confined to certain valleys in the Andes, between 1,000 and 12 000 feet above sea level, in which sometimes every individual in the whole community is, or has been, infected New-comers to these valleys almost invariably become infected and suffer the acute febrile attack, and frequently die

The disease appears after the rainy season when insect life is most abundant and malaria is rife

Persons of all ages are affected but the disease is much milder in children, and is probably often unrecognized

ÆTIOLOGY

The causal organism —*Bartonella bacilliformis* has two forms, a small bacillus like form 1μ to 2μ in length which may show branching and an ovoid form about 1μ in mean diameter It stains well with Romanowsky stains taking a blue colour (*see* plate B F)

It can be grown in Vervoort's medium used for the cultivation of leptospira, but does not grow easily It is suggested that the different stains of *Bartonella* vary in their ability to grow in culture medium

They are found in the red cells in the peripheral blood in an acute case, and in the endothelial cells of the capillaries in post-mortem or biop[illegible] tissue

[illegible]

and *muris*, by the dog flea and the rat-louse, [illegible]

Sources of infection —Man is probably [illegible] As bartonellæ are occasionally found in the [illegible] of symptoms, or even some time after [illegible] seem necessary to suggest an animal [illegible] other wild animals are susceptible to [illegible] reservoirs of infection, though [illegible]

PATHOLOGY

The general reaction produced is the result of bartonella invasion [illegible] the arteriolar endothelium and reticulo-endothelial cells of the lymphat[illegible] tissues, and of the blood destruction, much red cell debris has to be di[illegible]posed of, and there is very great anæmia

Lymphatic glands are often enlarged, and the spleen usually, an[illegible] there is a deposition of dark-yellow pigment in most of the organs, whic[illegible] gives the reactions of melanin There are often petechial hæmorrhages i[illegible] the mucous membranes and in some of the viscera

The endothelial cells of the arterioles and lymphatic channels ar[illegible] invaded by the bartonellæ, and the lumens of the channels are ofte[illegible] blocked, so that necrosis or œdema may occur Necrotic areas are ofte[illegible] seen in the spleen, and also in the liver, in the central part of the lobules

The bone marrow shows a marked hyperplasia, both of the erythro[illegible]blastic and the leucoblastic elements

In the local lesions there is blocking and dilatation of the vessels wit[illegible] the production of a hæmangiomatous condition There is proliferation o[illegible] the endothelial cells lining these blood sinuses, in these cells, bartonellæ may be found, but they are not numerous There is much new blood vessel formation The lymph channels are also obstructed, and the blocked vessels are surrounded by an area of infiltration, in which lymphocytes plasma cells, and fibroblasts take part

Blood picture —The red cell count may be reduced to less than a [illegible] the red cells are on the [illegible]

The leucocytes will be increased, often up to 20,000 per c mm, the proportions of the various types being maintained at about the normal

SYMPTOMATOLOGY

Discussion —The view that Oroya fever and verruga peruana are manifestations of the same infection is now generally accepted There is considerable parallelism between this disease and kala-azar, a condition in which an acute visceral disease may be followed by a generalized dermal eruption

In Oroya fever, if the patient dies from the acute febrile disease, he naturally does not suffer from the dermal lesions if he has a very severe [illegible] may be stimulated [illegible] h case he will not [illegible] hand if he has a [illegible] to such an extent, the bartonellæ which are taken up by [illegible] thelial cells in the skin and/or subcutaneous tissue will later multiply, and these will give rise to secondary lesions

The initial attack may thus be (*a*) severe and fatal, (*b*) moderately severe, (*c*) mild or (*d*) asymptomatic *The secondary lesions* will follow in (*b*), (*c*) and (*d*), probably in an ascending order of frequency

Recently, Tyzzer and Weinman (1939) have divided bartonellæ into two genera, *Bartonella* and *Hæmobartonella*, both are found in the blood

but the former produces nodular lesions in animals, whereas the latter remains in the blood and produces anæmia, but not skin lesions

If this applies in the case of bartonella infection of man, another explanation for [illegible] be given, namely, that each infect [illegible] and that one or more strains of [illegible]

The febrile attack —The incubation period is usually considered to be about three weeks

There is no dramatic onset but the symptoms develop rapidly with malaise, irregular intermittent fever usually rising to between 100° and 102°F, vomiting hiccough and progressive anæmia There is headache, pains in the joints and bones, and great tenderness of the bones, particularly those in which there is active marrow, the sternum, ribs, etc, this suggests some association with the observed hyperplasia of the marrow

Most of the other symptoms are the result of the rapidly developing anæmia and need not be detailed here Hæmorrhages into the skin and from mucous membranes and diarrhœa are common terminal symptoms

The course of the disease is very rapid and profound anæmia with red cells as low as 1 000 000 per c mm, may be produced within a week or even less, death usually results in two or three weeks, but may be postponed for several weeks On the other hand after a week or so the temperature may subside completely, the acute symptoms disappear, rapid regeneration of blood may take place and the patient may recover completely, in such cases the verruga eruptions may or may not follow within a few weeks

The mild and asymptomatic types —In the milder type, there are malaise, headaches pains in the bones and joints, possibly gastro-intestinal disturbances, and an intermittent fever The fever usually subsides a few days before the appearance of the eruptions which may be postponed as long as sixty days

The disease always runs a milder course in children and in them it may be symptomless, it is probably this fact that accounts for the comparative immunity of the local population in endemic areas

Persons with bartonellæ in their peripheral blood may show no symptoms whatsoever These persons may later develop verruga lesions

The dermal lesions or verruga peruana —There are two types of lesion, (i) the miliary granulo-angiomatous eruption, and (ii) subcutaneous nodule

The 'miliary lesions start as small sessile papules, usually on the sites of petechial spots, and increase in size up to that of a split pea, [illegible] in crops so that [illegible] lour, the lesions [illegible] cases in which [illegible] they are at first [illegible] progressing they [illegible]

they are p [illegible] legs, and c [illegible] and very [illegible] numerous so that in places they may coalesce [illegible]

The eruption may last for four or even six months, and a few cases have been reported in which they lasted as long as two years When they disappear they leave no mark

The **nodular** lesions have very much the same consistency as the papules but usually they are softer They may grow to the size of a pigeon's egg The commonest sites are on the extensor surfaces of the extremities The skin is stretched over the nodule, this may be normal in colour, but, if taut, it usually has a pinkish colour

When this nodule is on or near the knee, or on some other place where it is likely to be damaged, it may ulcerate and form what is known as a 'mular' lesion (apparently for the rather naive reason that mules suffer from a similar lesion), the mular lesion is a nodule with a fungating cap like the crater of a volcano and it is very liable to secondary hæmorrhage

Diagnosis —This presents few difficulties even from a clinical point of view, and is easily confirmed by finding the bartonella infection in the red cells in the febrile stage, or in the reticulo endothelial cells of the dermal lesions In the latter, parasites are always present, but are not abundant Escomel (1938) advocates cultural methods as being more certain

Treatment —There is no specific treatment that has any established reputation An arsenic antimony preparation, Bayer 386B, is apparently effective in the treatment of rats infected with bartonella, in these animals it is given in doses of 0 2 mg per kilo It is said to have been used with success in 14 cases of the disease in man

Treatment in the past has mainly been aimed at maintaining the patient's strength, and providing all the necessary materials for blood regeneration From the nature of the blood picture and from the fact that there is no actual loss of hæmoglobin outside the body, liver extract will obviously be more valuable than iron for this purpose

Prevention —In the absence of exact knowledge of the ætiology no general preventive measures have been adopted in the endemic areas From a personal point of view, the first important measure of prevention is to avoid spending a night in a known endemic area If this is not possible then since the disease is almost certainly transmitted by a biting insect protection at night by a sand fly net must be provided

Prognosis —Inhabitants of infected villages seem to acquire an immunity, but probably many die in childhood from the infection

In foreign visitors to such a village infection appears to be almost certain and the death rate amongst those infected is of the order of 50 per cent

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YELLOW FEVER

Definition —Yellow fever is an acute specific fever of varying severit but *characteristically one of great intensity* and associated with tox jaundice and albuminuria, it has a limited tropical distribution, and i caused by a filtrable virus which in the urban, either epidemic or endemi form of the disease is transmitted from man to man by aedes mosquitoe and in its jungle form is transmitted from its jungle reservoir to man b other means

Introduction —The importance of yellow fever to India and countrie further east lies in the fact that though the disease has up to the presen never appeared in these countries the why it should not invade them at son history of this disease shows that it and in the American continent, from which were previously free from it In India the stage is appa for an explosive epidemic should the virus ever be let loose here It i therefore essential that we in this country should take every precaution t prevent this catastrophe and if this invasion ever occurs we should b ready to deal promptly with any isolated case that appears, in order tha we may stamp out the disease before it gets a firm footing

In this matter, India has not only herself to consider but she has special mission in being in the front line in the defence of the rest of Asia she has not only her but th thousand million or s r wer to gain an effective that i would sweep through the rest of tropical Asia, and in these sanitarily backward countries there would be little hope of controlling it until it ha run its course and decimated the populations of this and other easter tropical countries

Whilst yellow fever is a disease that has from time to time extende its domain it is, on the other hand, one that has been very effectively con trolled in many countries where it was firmly established and had becom a serious menace to the community Yellow fever has always been hel an example of how medical research having shown the way, sanitary been brilliantly success one time the hope wa riumph over this disease have

India's problematical safeguards.—It was at one time suggested that there are probably minor differences in the aedes mosquitoes of this country, which make them incapable of transmitting yellow fever, this has been shown not to be the case, for aëdes collected in India have been used in transmission experiments and have been shown to be capable of transmitting the infection

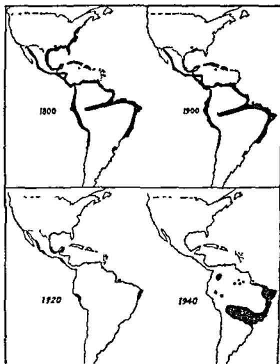


Figure 86 demonstrating three phases in the history of yellow fever in the American continent

Phase 1.—Between 1800 and 1900 the disease almost entirely disappeared from the United States, largely as a result of general sanitary improvement

Phase 2.—The complete disappearance from the United States and the reduction in Central and South America between 1900 and 1920 was due to the application of the knowledge that the mosquito *Aedes ægypti* was the main transmitter, and to measures directed against this insect

Phase 3.—The apparent extension of the disease between 1920 and 1940 is really an extension of our knowledge of the disease, with the discovery of jungle yellow fever

A second hope namely, that dengue or some other similar widespread infection, might have produced immunity to yellow fever in our populations, has also been abandoned after the discovery that of the many hundreds of samples of blood collected in various parts of India, none showed any evidence of *immune bodies*

We are thus thrown back on the vague hope that as yellow fever has not appeared hitherto, there must be an unknown factor some special local condition, which prevents its gaining a footing

It is not necessary to introduce this 'unknown factor', for the explanation may be that the virus has never arrived in this country, either in an infected individual or in a transmitting mosquito but because this has not happened in the past there is unfortunately no guarantee that it will *not happen* now or at some future date This danger is vastly increased by the enhanced speed of transport generally, and particularly by the increase in aerial communications between the yellow-fever areas and the rest of the world The only safeguard then is increased *watchfulness to prevent either an infectious patient* or an infected mosquito from arriving in this country, the measures that are in operation to effect this will be described below

Historical.—There is evidence that the disease has existed on the American continent from the time of Columbus; a serious epidemic is reported as early as 1493 in San Domingo There are many early references to a disease that was undoubtedly yellow fever, from this date onwards, and in the eighteenth century it was so well known that quarantine regulations were introduced in connection with it It was endemic over a much wider area in earlier days, but it had disappeared from many old endemic areas, even before the exact mode of transmission was known,

presumably as a result of the introduction of general sanitary measure In America, epidemics were reported as far north as New York an Philadelphia, but during the last fifty years only one epidemic of an importance, the epidemic in New Orleans in 1905, has occurred in th United States In its eastern sphere, it was at one time apparently rife i Spain, including Gibraltar, in the Canary Islands, and all along the we African coast

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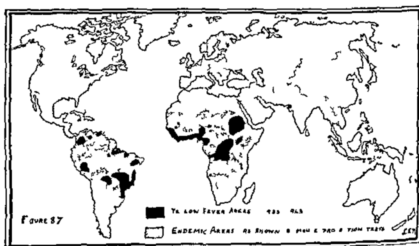
that landed in the West Indies was almost completely destroyed by yellow fever

In 1881, Carlos Finlay, a Cuban of Anglo-French parentage, suggeste that the disease might be transmitted from man to man by mosquitoe and carried out experiments to demonstrate this However, this mean of transmission was not generally accepted until, Ross' work on malari having led to a reconsideration of Finlay's theory, the historical experi ments were carried out in 1900 by the American yellow-fever commissio *consisting of Walter Reed, James Carroll, Jesse Lazear, and Aristide* Agramonte They demonstrated the aëdes transmission, and furthe showed that yellow fever was not transmitted by contact or other means Lazear died of yellow fever, and Carroll developed yellow fever after bein bitten by an infected mosquito in an experiment, but recovered As a resul of these observations, control measures were instituted against aede mosquitoes in Central and South America, and by 1920 the incidence o

ng point (*vide* figure 86)

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EPIDEMIOLOGY

Geographical distribution—Yellow fever is now confined almost entirely to the tropics Most of the endemic areas are on the Atlantic sea-board, though in South and Central America some parts of the pacific coast are included and in Africa the endemic areas extend from the west coast for some thousands *of miles inland*

In the Americas only one outbreak of urban yellow fever has occurred

from Senegal down to Angola and inland as far east as the Anglo Egyptian Sudan Uganda and Tanganyika and even into Abyssinia An epidemic in the Nuba Mountains in the Sudan which has been recognized as a silent area for some years has recently occurred (*vide infra*)

There are no endemic areas on the east coast of Africa nor anywhere in Asia

Epidemic features —From an epidemiological point of view there are two forms of the disease the urban and the jungle The urban form is usually endemic but it may be epidemic especially when new territory is invaded The jungle form is usually sporadic but may also become epidemic

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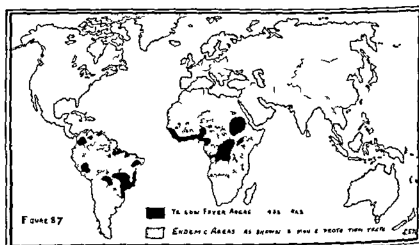
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cases of death through an uncertain cause a specimen is taken and examined microscopically (*vide infra*) The mouse protection test is a test to show the presence of protective antibodies in the blood and a positive result indicates that the patient has at some time suffered from yellow fever These two methods have shown the existence of the disease in many parts of South America and Africa where its presence was hitherto not suspected and the findings have usually been confirmed later by the discovery of clinical cases In Africa in certain areas in the Sudan for example many protected individuals have been discovered though the disease has never been reported These have been called *silent areas* and recently in one such area in the Anglo Egyptian Sudan *i e* in the Nuba Mountains near Malakal the silence has been broken by an explosive epidemic In known endemic areas
epidemic form for many years chil
not shown positive protection tests
have provided a large percentage

presumably as a result of the introduction of general sanitary measures In America, epidemics were reported as far north as New York and Philadelphia, but during the last fifty years only one epidemic of any importance, the epidemic in New Orleans in 1905, has occurred in the United States In its eastern sphere, it was at one time apparently rife in Spain, including Gibraltar, in the Canary Islands, and all along the west African coast The disease played an important part in naval and military history in the sixteenth century Drake's fleet was badly infected after calling at West Coast and Spanish ports, and in 1800 a Napoleonic army that landed in the West Indies was almost completely destroyed by yellow fever

In 1881, Carlos Finlay, a Cuban of Anglo-French parentage, suggested that the disease might be transmitted from man to man by mosquitoes and carried out experiments to demonstrate this However, this means of transmission was not generally accepted until, Ross' work on malaria having led to a reconsideration of Finlay's theory, the historical experiments were carried out in 1900 by the American yellow-fever commission consisting of Walter Reed James Carroll, Jesse Lazear, and Aristides Agramonte They demonstrated the aedes transmission, and further showed that yellow fever was not transmitted by contact or other means Lazear died of yellow fever, and Carroll developed yellow fever after being bitten by an infected mosquito in an experiment, but recovered As a result of these observations, control measures were instituted against aedes mosquitoes in Central and South America, and by 1920 the incidence of the disease had been reduced almost to vanishing point (*vide* figure 86)

Aedes ægypti was first the only mosquito incriminated, later, other aëdes were shown to be potential transmitters, then followed the discovery of 'jungle' yellow fever, with its tremendous implications jungle mosquitoes, notably *Hæmogogus capricorni*, were incriminated as transmitters, with some jungle animal, possibly monkeys, as the reservoir of the virus


Figure 87

EPIDEMIOLOGY

Geographical distribution—Yellow fever is now confined almost entirely to the tropics Most of the endemic areas are on the Atlantic sea-board, though in South and Central America some parts of the pacific coast are included, and in Africa the endemic areas extend from the west coast for some thousands of miles inland

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rom Senegal down to Angola ar
Egyptian Sudan, Uganda, and Tan
epidemic in the Nuba Mountains in the Sudan, which has been recognized as a 'silent area' for some years, has recently occurred (*vide infra*)

There are no endemic areas on the east coast of Africa, nor anywhere in Asia

Epidemic features —From an epidemiological point of view, there are two forms of the disease the urban and the jungle The urban form is usually endemic, but it may be epidemic especially when new territory is invaded The jungle form is usually sporadic, but may also become epidemic

disease of
by jungle
vns where,
and then
endemic

The epidemiology of the disease has recently been studied in two ways, by viscerotome surveys, and by the mouse-protection test (*see* p 299)

The viscerotome is an instrument which has been designed for removing pieces of liver without a full post mortem examination, in all cases of death through an uncertain cause, a specimen is taken and examined microscopically (*vide infra*) The mouse-protection test is a test to show the presence of protective antibodies in the blood, and a positive result indicates that the patient has at some time suffered from yellow fever These two methods have shown the existence of the disease in many parts of South America and Africa where its presence was hitherto not suspected, and the findings have usually been confirmed later by the discovery of clinical cases In Africa, in certain areas in the Sudan for example, many 'protected' individuals have been discovered, though the disease has never been reported These have been called 'silent' areas and, recently, in one such area in the Anglo-Egyptian Sudan *i e* in the Nuba Mountains near Malakal, the 'silence' has been broken by an explosive epidemic In known endemic areas
epidemic form for many years, chil
not shown positive protection tests,
have provided a large percentage
places distant from the yellow-feve
been found in the blood of the inhabitants

Season and altitude —High temperatures, 75°F and above, and high humidity favour the spread
to coastal areas in the true
the hot damp months of the
though it has been reported

of
of
and
em
in

ÆTIOLOGY

Historical—Many organisms have been isolated from patients and presented as the cause of yellow fever, but the classical mistake of Noguchi is the only one worth recording as Professor Noguchi was a brilliant worker who was led down the wrong path by a clinical mistake—not his own, for he was not a doctor He isolated a leptospira from cases presented to him as yellow fever, and named it *Leptospira icteroides* It was in fact *Leptospira ictero-hæmorrhagiæ* the causal organism of Weil's disease, which was the disease that these patients were really suffering from Noguchi died of yellow fever whilst carrying out experiments in West Africa where, dealing now with true yellow fever, he had entirely failed to confirm his earlier findings—a tragic sequel to perhaps the first mistake of a brilliant investigator

Meanwhile, Adrian Stokes (who later died of yellow fever) Bauer, and Hudson infected Indian monkeys with yellow fever by means of blood filtrates of patients, and thus proved that the disease was caused by a filtrable virus they further demonstrated that very small quantities of the serum of yellow fever *convalescents protected a monkey*

The virus—This is a filtrable virus, of the size of about 18 to 27 micro-microns ($\mu\mu$) : it is killed at 60° to 65°C, but survives freezing in *vacuo* for many years It also withstands the action of some strong dis- [illegible] C, but is inactivated by the photo- [illegible] in 100,000 Like other filtrable [illegible] iving tissues

Tropism.—The virus may be, (i) viscerotropic (or pantropic)—as in the patient with *yellow fever or in animals inoculated subcutaneously or* intra-viscerally from such a patient, (ii) neurotropic—after serial inoculation in mouse brain, or (iii) atropic, *i e* free from any organotropism—after serial cultivation on nerve-free chorio-allantoic membrane There *is some ev* [illegible] *s may possibly revert to the* viscerotropi [illegible] but there is no evidence that egg-grown [illegible] or neurotropic tendency

Susceptible animals—The rhesus monkey and the mouse are most [illegible] the common monkey of the Indian [illegible] out other Asiatic, [illegible] ible, and certain [illegible] of yellow fever [illegible]

The European hedge-hog also is susceptible to the virus

Transmission—Infection is very easily acquired in the laboratory, and [illegible] contact with the blood of a patient [illegible] m experimental animals, before the [illegible] n, nearly every member of the staff [illegible] -fever laboratory developed yellow fever

The mosquito *Aedes ægypti* is the important transmitter of the urban form of yellow fever from man [illegible] been shown to transmit it under laboratory [illegible] *vittatus, africanus,* and *simpson* [illegible] in Africa, *Hæmogogus capricor* [illegible] *celænus,* in South America, and *Aedes albopictus*

The mosquito becomes infected if it 'bites' a patient during a period from the appearance of the first symptoms (and probably even earlier, as in the monkey the virus can be demonstrated within 12 hours of inoculation) up to *the end of the third possibly the fourth,* day of the disease, the virus infection develops in the mosquito for some days before the latter becomes infectious, the time varying between four and twenty-eight days according to the temperature at which the mosquito is kept, under natural *conditions in the endemic areas,* the average latent period is about twelve

days and from th

sporadically, monkeys have been shown to carry antibodies in their blood

Factors determining incidence—The incidence of the disease is conditioned by (a) the number of the vector mosquitoes, (b) the supply of the virus, and (c) the extent of the susceptible material

Aedes is a domestic mosquito and thrives best in towns In the urban form man is the only source of infection, and it is probably mild and unrecognized cases of the disease that are the most important source of the virus The highest concentrations of (a) the transmitter, (b) the source of infection, and (c) susceptible individuals are found in towns and it is therefore here that the epidemics usually occur

Immunity—There is no natural immunity to this infection Popula-

in earlier life, when the symptoms may be overlooked The presence of

Mouse protection test—When

and 25 children should be chos

taken from each and the serum

is mixed with 1.5 c cm of a

infected with the neurotropic v

intraperitoneally into six mice

injection of 0.03 c cm of 2 per

Observe for 10 days if more than three survive the test is positive but if four or more die it is negative that is no immune bodies are present

By diluting the serum further an exact quantitative test is possible which

of blood in the first instance

PATHOLOGY

Morbid anatomy—The typical post-mortem picture includes the olive discoloration of the skin (in the fair-skinned races) and of all the organs and tissues, ecchymoses all over the body, especially at pressure points,

Histological examination of sections of the liver shows characteristic changes that are usually far more extensive than the gross appearance of the organ suggests Th[illegible]
degeneration These
ones are cloudy swell
necrosis of the liver p

One of the earliest changes is a finely granular appearance of the cytoplas[illegible]
is lost
yellow fe
so that, as the degeneration progresses, large droplets appear The fatty changes appear to be complementary to the necrosis, being more apparent in the non-necrotic portions of the liver

The cytoplasm undergoes coagulative necrosis, it may become vacuolated, and hyaline eosin-staining areas appear, chromatolysis occurs in [illegible] r than normal, there is at
then red acidophil bodies

[illegible] Councilman cell
in which the full range
[illegible]

bodies appear

The extent of the parenchyma involvement will vary from 5 to 95 per cent, in the latter case, only a few areas around the portal sheaths at the periphery of the lobule and around the central vein remain intact, and even these usually show some cloudy swelling under such conditions

These changes account for the t

In the kidneys there is cloudy
apparent in the convoluted tubul
hæmorrhages into Bowman's capsule and in the cortex, and the tubules are blocked with epithelial debris These changes readily explain the albuminuria and the eventual anuria

The spleen shows few macroscopical changes but microscopically there is evidence of endothelial proliferation at the expense of the lymphoid tissue

to bear the brunt of the attack

The pathology in the jungle form of yellow fever is apparently identical with that of the classical form

Blood picture and blood chemistry—There is a leucopenia during the early stages up to the fifth or sixth day, after which there may be a slight leucocytosis During the first few days there is a lymphopenia which gives place to a granulopenia later, there is a relative increase of large mononuclears

Very early there will be an increase in hæmobilirubinæmia (*indirect* van den Bergh test positive), and later, when jaundice develops, bili-

SYMPTOMATOLOGY

Clinical types.—All degrees of severity will be encountered and division into types is artificial but will perhaps facilitate description

(i)

a few ho

of attack

severity, the presence of albumin in the urine and the slowing of the pulse in convalescence should raise suspicion as to its true nature

During an epidemic, *e g* the Nuba Mountains outbreak, there is often evidence that about 70 per cent of the attacks are apparently sub clinical, but it is probable that, if those natives who showed a positive mouse-protection test could have been observed closely the majority would have shown a mild febrile attack of this kind

(ii) *Incomplete attack*.—There is a sharp rise of temperature with

infection, but, in the case of laboratory infection, instances where the

pains all over the body but particularly in the loins and bones, an intense burning sensation and dryness of the skin a furred sharp-pointed tongue with a pink tip and edges a red and swollen face with the eyes bloodshot and 'beady', anorexia and severe prostration

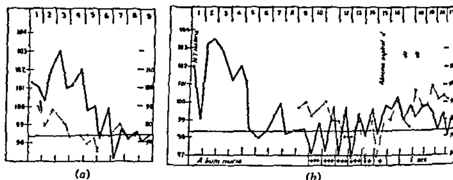
increases, there are hæmorrhages from mucous membranes, into serous cavities, and subcutaneously especially into the scrotum and vulva and at pressure points, and eventually there may be anuria

In fulminant cases the early febrile stage will merge into the toxæmic stages without the characteristic interlude

Termination.—Death may occur in the febrile stage from hyperpyrexia with delirium or in the 'period of calm' and be associated with profuse hæmorrhages from all mucous membranes, with black vomit, melæna and hæmaturia the patient passing into a comatose state Death seldom occurs

before the third day or after the eleventh, and if the temperature is down *by the seventh day* the prognosis is good

The fever —The temperature rises sharply, reaching 103°F or higher in 24 hours and remains high for three or four days, it then falls usually rather rapidly and may become sub normal for 24 hours—the 'period of calm', but it may rise again to 101° or 102°F for another two or three days or more (*see* charts, figure 88)



(a) (b)

Figure 88 Two yellow fever temperature and pulse charts
(a) A relatively mild case
(b) A case complicated with malaria and abscess formation (Kirk *et al* 1941)

The pulse —This is rapid full and bounding at first, but the pulse rate tends to
lower du
level du
temperat ... onstant temperature constitutes
Faget s s ... importance

Jaundice appears on the third or fourth day and is progressive—up to a dark brown colour in severe cases Its earlier appearance suggests a bad prognosis It is a common but not a constant sign and even in *moderately severe cases it may not be prominent It is naturally* associated in severe cases with bile in the urine and a bi phasic van den Bergh reaction

Petechial hæmorrhages may appear, and a characteristic erythema of the scrotum or vulva is common *In severe cases large purpuric patches appear*

Other symptoms —Insomnia and restlessness are constant but delirium is rare except as a terminal condition Vomiting may occur with the onset of the fever, as with any high fever, but the characteristic severe vomiting occurs from the third day onwards and may assume a coffee-ground character, the typical 'black vomit' of yellow fever, which always portends a grave issue

DIAGNOSIS

A The clinical diagnosis —The clinical diagnosis of a typical case presents little difficulty The sequence of events is very characteristic, there ... stage and

until anuria supervenes, ...

Even if jaundice is slight during the course of the disease, it will in every fatal case be marked at the time of death

During the presence of a recognized outbreak, the occurrence of mild fever of two or three days' duration associated with a disproportionate degree of headache and the presence of albuminuria will lead to a suspicion

of yellow fever In an isolated case of the mild type, it will be almost impossible to make a clinical diagnosis

B *Laboratory diagnosis* Tests for the presence of yellow-fever

virus infections also cause
ould be controlled by pro-
serum Blood taken for
the ice-chest more than a

less certain

Tests for the presence of immune bodies —When, in the later stages of

so that mosquitoes are not usually infected after the third day of the disease, for purposes of the mouse protection test the antibodies are seldom present in sufficient quantity to ensure a positive result before about the twenty-first day, the diagnostic value of this test is thus limited (For technique *see* p 299)

fever

C *Post-mortem diagnosis* —The characteristic changes in the liver enable a post-mortem diagnosis to be made by naked-eye and histological examination

Portions of the liver can be taken for the purpose by carrying out a full post-mortem examination or, when this is not permitted, by removing a piece by means of the viscerotome, the instrument devised for removing

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x with
which
st into

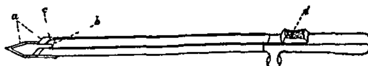


Figure 89 The viscerotome

a Cutting edges for introducing viscerotome
b Sliding guillotine blade
c Groove for sliding guillotine blade
d Thumb grip for closing the sliding guillotine blade

a solid organ, the three fixed blades make a deep U-shaped incision, the flexible blade is moved forward, completes the open side of the U to make a more-or-less square incision and then, dipping downwards behind the rectangular block of tissue to meet the lower blade, it severs a piece from the rest of the organ and encloses it in the viscerotome, the instrument is then withdrawn, opened, and the contained piece of organ removed

Technique —The entry point of choice is in the epigastrium just below the ensiform cartilage and close to the costal margin on the right side The direction of the thrust is at an angle of about 10° with the horizontal and about 20° with the body surfaces from left to right (figure 90) The instrument which must be closed (figure 91*a*) is pushed through the skin and the abdominal wall with a sharp thrust When the lower fixed blade has penetrated the liver the flexible blade is opened about an inch, the instrument is thrust further into the organ for about half an inch and then the flexible blade is pushed forward again and held firmly in this position while the viscerotome is withdrawn from the body

The flexible blade is withdrawn and the piece of liver removed and placed in solution for subsequent sectioning

The hole made by the instrument is now plugged with cotton wool to prevent oozing and the skin wound is sewn up if this is considered necessary The warning may seem superfluous but it must be emphasized that this viscerotomy is only a *post mortem procedure*

Differential diagnosis —The most constant and prominent symptoms of yellow fever are fever and jaundice, therefore the diseases with which it is most likely to be confused are severe malaria of the 'bilious remittent' type blackwater fever, Weil s disease infective hepatitis, and catarrhal jaundice Certain fatal liver conditions such as acute yellow atrophy and carbon tetrachloride poisoning might be mistaken for yellow fever in the latter the hepatic necrosis is central The milder forms of yellow fever might be confused with relapsing fever, dengue, or influenza

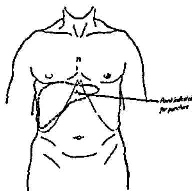


Figure 90 Showing point of entry and direction of thrust of the viscerotome

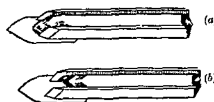


Figure 91 Viscerotome (*a*) shut and (*b*) open

In the malarial fevers the parasite should be easy to demonstrate, while the jaundice appears earlier and tends to improve, in blackwater fever parasites may not be found but the hæmoglobinuria of this condition should not be mistaken for the hæmaturia of yellow fever Similarly, in relapsing fever the spirochæte is usually found in the peripheral blood The saddle back temperature of dengue is not unlike that of yellow fever but the dengue rash when present is characteristic, and jaundice does not occur

The only real difficulty that is likely to arise is in differentiating Weil s disease, and in this case we have the precedent of Noguchi s classical mistake (For the exclusion of Weil s disease see p 251)

Precautions —If there seems to be a serious possibility that the case is yellow fever, the utmost precautions must be taken immediately and the patient kept rigidly under a mosquito net day and night Also it should be remembered that the virus is present in the patient's blood and is

unneutralized by antibodies for at least three and in some cases up to four days, and that therefore every care should be taken to prevent his blood touching anyone's unprotected skin during the process of blood withdrawal (In most countries immediate notification to the health authorities is imperative)

PREVENTION

For the disease to be spread, there are three requirements—the virus, the transmitting mosquito, and the susceptible population

The main successes in yellow fever prevention in the endemic areas have been achieved by aedes control Aedes is a mosquito which is very local in its habits, it bites during the day, so that thorough spraying of

population, very careful inspection at frequent but irregular intervals is essential It has been found that, provided the aëdes index is reported below 2 per cent (that is, only 2 per cent of houses inspected show aëdes breeding places), yellow fever will not spread

Aëdes seldom flies more than a few hundred yards from its breeding place, and therefore control for an area of four hundred yards around a house, or aerodrome, is usually considered sufficient Similarly, if ships are moored a quarter of a mile from the shore in a yellow-fever port, they are considered to be safe, but this does not take into account the danger of mosquitoes being brought from the shore in small visiting craft, or in coal or other lighters

It is beyond the scope of this book to describe in any detail the procedures that should be adopted against these mosquitoes, but besides the elimination of breeding places and other anti-larval measures and the destruction of the adult mosquitoes by spraying (*vide* p 115), for personal protection some deterrent application should be smeared on the ankles, wrists, neck and other exposed parts of the body For this purpose the following makes an effective cream (*see* also p 119) —

Citronella oil	8 parts	Soft paraffin	57 parts
Camphor	1 part	Hard paraffin	29 parts
Liquid extract of pyrethrum	5 parts		100 parts

Another measure that is now being adopted with increasing frequency in several countries is the reduction of the susceptibility of the population at risk by prophylactic inoculation

History of yellow fever vaccination —Hindle in 1928 suggested prophylactic inoculation, and Sawyer *et al* (1931) introduced sero-vaccination which consisted in giving an emulsion of the liver of an infected monkey in combination with convalescent serum, the latter prevented the development of the disease, but

been carried out

The vaccine is made from a strain which was originally a virulent pantropic virus that had been passaged some hundreds of times on mouse-embryo tissue-culture medium until it completely lost its viscerotropic

qualities and became a neurotropic virus · then it was passaged agai some hundreds of times, on chick embryo from which the brain and spina cord had been removed, so that it lost its neurotropic qualities The firs virus thus made caused no serious trouble, but an appreciable percentag of those inoculated suffered from jaundice, this was possibly due to a *accidental* contamination with some other virus The present strain i entirely innocuous, the injection is not followed by any local or genera reaction*, only one injection of 0 5 c cm (1,500 mouse-protection units) i necessary, and it produces an immunity which is protective from the tent day and lasts for a considerable time—there is some diminution in th protective power of the blood at the end of four years, and revaccination i recommended after this interval

All persons dealing with yellow-fever patients or infected animal *their blood or excreta, or the preparation of vaccines, should be inoculated* In South America and Africa, [illegible] especially in areas where the [illegible] is no other measure of control [illegible] be used in these circumstances

Special measures in India.—In this country, the susceptible populatio [illegible] ively uncontrollable [illegible] the third direction [illegible] nsideration must b

Towards this end a very great deal is being done Air traffic has introduced a new source of danger and it is on this that most attention is now being centred, though other possible channels of entry, *e g via* Bombay and other west coast sea-ports where for many years precautionary measure have been in force, are not being forgotten

We must first return to Africa The planes from Lagos on the West Coast, after passing through active yellow-fever areas, join the Cape-to-Cairo route at Khartoum There is a considerable amount of air traffic from Lagos to Khartoum and thence to Cairo It is thus obvious that a person could get on board a plane at Lagos in the early stages of the incubation period of yellow fever, change at Khartoum, again at Cairo where he could pick up the regular service plane from Europe to India and reach Karachi even before symptoms had developed Further Malakal, an aerodrome in the Anglo-Egyptian Sudan on the Cape-to-Cairo route, has long been recognized as a 'silent' yellow-fever area, for a large percentage of the population have antibodies in their blood, as shown by the mouse-protection test, and from time to time suspicious cases have been reported Such 'silent' areas are potential dangers, and from them an infected person might arrive in India at an even earlier stage It was therefore laid down by the International Sanitary Convention for Aerial Navigation that, for purposes of this convention, 'silent areas' shall be treated as yellow-fever areas

[illegible] achi whenever a passenger [illegible] from [illegible] all necessary precautions may [illegible] are allowed to come to

* Recently, an infective hepatitis has recurred amongst U S A troops that had received prophylactic injections from certain batches of yellow fever vaccine The first symptoms appeared between 40 and 100 days after vaccination and the resultant invalidism averaged two months Official figures are naturally not yet available but [illegible] many thousands of soldiers wer [illegible] two per thousand of hospital [illegible] but a contaminating virus that [illegible] tion of the infected batches [illegible] and the accident is not likely to recur

Karachi from the endemic or 'silent' areas unless they have passed through either Khartoum or Cairo, which are anti-amaryl aerodromes [that is to say, especially equipped for anti-amaryl (anti-yellow-fever) measures, which include local control of aedes mosquitoes and 'disinsectization' of the aeroplanes before they leave], and unless they carry a certificate of disinsectization from a competent authority in one of these two places For disinsectization 'pyrocide 20', a pyrethrum spray with a kerosene base, has been used, but there are similar preparations with watery bases which are safer and almost, if not quite, as effective (see p 116)

In India, the further precautions that are taken include the following:—

inside of the plane is carried out before is removed

a 'disinsectization' certificate, it will be all persons on board other than those who have been protected against the disease by a previous attack or by satisfactory inoculation, will be subjected to isolation for a period not exceeding nine days from the time of arrival of the aircraft

in India and

(ii) not more than two years before his departure from the yellow fever-infected area

(d) Finally, aircraft are prohibited from entering India from the west except at Karachi where the organization for carrying out these measures exists

The sanitary authorities in India have had a great fight with the international authorities to get these measures enforced in other countries, but they insisted on certain minimum requirements, which were eventually

to the present, has depended

It should perhaps be repeated that in no circumstances is one permitted to import yellow-fever virus into India, for any purpose whatsoever

Aedes ægypti also transmits dengue, and the rapidity with which this infection spreads gives one some idea of how yellow fever would spread if it once gained a footing in India Special measures are taken at aerodromes and in dock areas to control this species, as an extra precaution against yellow fever In the event of an invasion by yellow fever, aedes control would have to be given priority over all other sanitary measures throughout the whole country

ding some coming
olesale inoculation
vaccine are being

TREATMENT

There is at present no recognized specific for this disease, so that the treatment is essentially symptomatic The extreme variability in the

severity of the disease accounts for the innumerable specifics that ha
gained local reputations

The patient must be kept in a mosquito-proof room or under a n

and consist mainly of lime-whey, albumin water and barley water rie
of alkaline fluid should be given, *sodium citrate or bicarbonate, by mout*
if possible, otherwise per rectum Glucose should also be given liberall
by m ent solution together wit
one n cy to hypoglycaemia *
to reduce gastro-intestin
acidity is looked upon by some workers as a specific —

℞ Liquoris hydrargyri perchloridi		min xii
Sodii bicarbonatis		gr vi
Aquam	ad	℥i

Take hourly

— in doses of calomel half-hour
up t be avoided
ent stomatitis and parotiti
hydr

Other treatment is symptomatic —

Vomiting —Ten minims of adrenaline (1 in 1,000) by mouth or ¼ gra
of cocaine in an ounce of water

Black vomit —*Liquor ferri perchloridi, ♏xv, to be repeated*

Hyperpyrexia —This should be treated by hydrotherapy rather th
antipyretic drugs

Restlessness —Phenobarbitone, gr 1 to 3 by mouth or gr 1 intr
muscularly

Anuria —Dry cupping to loin, warm colon wash and warm citra
saline bladder wash, in addition to glucose and sodium bicarbona
intravenously

Stimulants may be required in the later stages, especially during th
'period of calm' when collapse is not infrequent

Convalescents should be treated cautiously, especially with referen
to diet which should be increased very slowly, indiscretion may hav
serious consequences

PROGNOSIS

The disease was at one time considered to be nearly 100 per cen
fatal, but later it was realized that, in indigenous populations in parti
ular, the infection often and that eve
Europeans in Africa suffer t be recognized
In most endemic areas, a suffering fro
definite clinical attacks of *the death rat*
will vary considerably according to circumstances, but in semi immun
populations it is undoubtedly sometimes a very mild disease, comparabl
to dengue *both in its severity and in its clinical manifestations* In th
recent epidemic in the Anglo-Egyptian Sudan, the mortality is reporte
to have been 10 per cent

It is however, an alarming disease when it occurs in epidemic form
and their utter helplessness to assist in any way the patient with a sever
attack leaves a lasting and horrifying impression on the mind of physician
who have been through an epidemic

* Recent work has shown the liver protecting value of a high protein diet with
choline It seems possible that the parenteral administration of the amino-acids
cystine and methionine might be even more advantageous than glucose in this disease

Addendum—No outstanding observations have been made during the last two years but the recent work on the reservoir of infection of jungle yellow fever has clarified the position (Bugher *et al.*, 1944)

where a continuous supply of fresh fuel was maintained In the jungle this is s p plied by migrating mammals and marsupials as well as by the newly born and it has been shown that jungle foci of infection tend to move from place to place

The infected jungle mosquitoes will survive for several months so that they are more truly the reservoirs of infection They may also migrate into coffee planta tions where they come into closer contact with man and may become the vectors in a small localized epidemic The greater danger is that a man who is sporadically infected in the jungle as frequently happens when tall jungle trees are cut down and the tree top dwelling *Hæmogogus capricorni* swarm around the woodmen will go into a town during the incubation period and start an *Aedes* born epidemic

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RIFT VALLEY FEVER

Definition —Rift valley fever is an epizootic hepatitis with a limited geographical distribution in certain circumstances it is transmitted to man in whom it causes a mild febrile disease

Discussion —The importance of this disease lies on the fact that it may be mistaken for mild yellow fever, because of its African distribution and because of the hepatitis It is a by a specific filtrable virus, of wh examples that have not yet achieved

Historical —Though a very similar disease was encountered in this locality ... now known was described ... s common d amongst ... ot c The developed lied of the

Epidemiology —The disease is so far confined to the Rift valley in Kenya and to those coming in contact with the infected cattle or sheep or with the virus in the laboratory

Ætiology —The disease is caused by a filtrable virus 23 to 35$\mu\mu$ in size which is found in the plasma and is attached to the red cells it is present for six days after the onset of the attack after which it is neutralized by antibodies that appear in the blood The virus has an affinity for the nervous system It does not appear in the urine

It is transmitted through the mucous membranes or the scarified skin. Mosquitoes of the genus *Mansonia* especially *Mansonia fuscopennata*, are suspected as carriers of the infection in nature

Immunity—There is immunity after an attack, which lasts for some years certainly six but is probably not permanent In animals it lasts only about six months

Pathology—The morbid anatomy has been studied in animals The most characteristic f [illegible]
but eventually coa
cytoplasm of the live

Blood picture—
attack and this is
lymphocytes

Symptomatology—The incubation period is from four to six days the onset is sudden, with rigors (often) malaise nausea headache and photophobia backache, and a feeling of fullness in the liver region The [illegible]

1

during convalescence

Diagnosis—A diagnosis can be made by inoculating the blood during the first few days into mice 0 1 c cm being given intraperitoneally, the mouse will develop an encephalitis in 48 to 72 hours As many other viruses kill mice the identity of the infection must be ascertained b [illegible]

A retrospective diagnosis can be made by the mouse protection test (*cf* YELLOW FEVER) or by a complement deviation test which remains positive for at least six months

The disease has to be differentiated from influenza dengue sand fly fever other forms of hepatitis and mild yellow fever

Prevention—A vaccine made from a fixed neurotropic virus has been used with success in prophylaxis in sheep

Treatment—No specific treatment for the condition has yet been discovered The symptomatic treatment consists in giving glucose freely by mouth and intravenously Convalescent serum is reputed to cut short an attack

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DENGUE SAND-FLY GROUP

Introduction —The two main clinical syndromes of this group are the mosquito borne dengue and the sand-fly-borne sand-fly fever Both diseases are caused by filtrable viruses, are clinically characterized by short fever, a rash, severe pains in the joints and back, and headache and are diseases of very low mortality Megaw, who was one of the first workers to insist on the recognition of this group as a group—a procedure which

Most workers however, who have had experience of both diseases, recognize the clear differences in the syndromes, and consider the two as quite separate diseases probably caused by two distinct viruses Admittedly, it may be very difficult in any one particular case to be dogmatic and say this is definitely a case of sand fly fever or of dengue but given half a-dozen cases of each disease it will usually be possible to say, quite definitely, which set is dengue and which sand fly fever Further, there is no evidence of the existence of any cross immunity

Megaw postulates a third member of this group—dengue of unknown vector Our knowledge of the short fevers of the tropics is certainly far from complete and a possible example of another disease of this group is so called … gin which, mainly on … by a tick … al 1940)



Figure 92 Temperature chart of Colorado tick fever (Topping *et al* 1940)

The dengue-like nature of this disease (*vide* figure 92) seems to be more certain than its suggested mode of transmission We must realize that the future may add more members to this group, … purpose and might imply the recognition of a single specific clinical syndrome whose full ætiology was unknown

DENGUE

Definition —Dengue is a short febrile disease of about 7 days' duration, characterized by severe pains all over the body, rashes, and a terminal rise of temperature It occurs endemically and epidemically in the coastal areas of many tropical and sub-tropical countries It is caused by a filtrable virus, and is transmitted from man to man by stegomyia (aedes) mosquitoes

Historical —Dengue has been recognized in various countries as a distinct …

… sufferer

In 1903 Graham transmitted the disease by the agency of mosquitoes which he des… … and Craig transmitted dengue in blood … They experimented with culex and … In 1916 Cleland Bradley and McDonald … A few years later Siler Hall and … these observations and demonstrated the whole transmission cycle (*vide infra*)

EPIDEMIOLOGY

Geographical distribution —It has a wide, tropical and sub tropical distribution in the four major continents, and it occurs in Queensland in Australia In America except for a few isolated epidemics, e g the ' extends from Charleston in South

therefore confined mainly to coastal areas distribution of aedes, and it is

Epidemic features —It is a disease of towns rather than country areas It does not occur at an altitude of more than 6,000 feet and it is confined to the plains in the sub-tropical regions In the tropics, it is endemic but subject to cyclical and seasonal exacerbations, in the sub tropical and temperate zones it is usually epidemic (e g the epidemics in Dallas in 1897 and in Athens in 1927 when at least half the inhabitants suffered and the public services were temporarily dislocated)

Seasonal incidence —In the sub-tropics, it is a late summer and autumn disease In the tropics it is variable and again dependent on aedes activity in many places, it is perennial, but it tends to show a monsoon rise and in Calcutta the highest incidence is in August and September

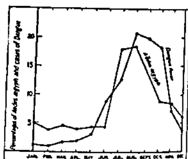


Figure 93 Seasonal curves of aedes and dengue in Calcutta

Age sex and race —All ages and both sexes ... is les ... are ... inhabitants nearly always enjoy some if not complete immunity through previous infection it is always the visitors who are attacked Every year we have half a dozen or more cases amongst our post graduate students, and the patients are always the visitors to Bengal though such students represent only a small percentage of the class

ÆTIOLOGY

The virus —Th ... land fi ... disease ... pass through L_3 and L_5 Chamberland filters ... blood for the first three days of the ... antibodies

T ... as *Ste* ... *Aedes ægypti* (previously known ... infectious after biting a patient within the first three days of the fever the virus undergoes development in the mosquito, which is capable of transmitting after the 8th day and remains infectious for the rest of its life *Aedes* alone transmits, not *Culex* In the Philippines *Aedes albopictus* is the transmitter

Immunity —An attack causes a certain amount of immunity, but not complete immunity The first attack is usually a bad one, the second is a mild one, and the subsequent ones are usually abortive amounting to little more than a feeling of malaise for 24 hours or less and possibly being unnoticed Recent work shows that there is no cross immunity with sand-fly fever or yellow fever

PATHOLOGY

Dengue is not a fatal disease, so that little is known about the morbid anatomy

The **blood picture** has certain characteristic features, there is marked leucopenia, which is a granulopenia The Arneth count shows a marked

shift to the left There may be a distinct leucocytosis following the attack, with the Arneth count still maintaining its leftward shift

There is nothing characteristic in the urine, it is highly coloured and there is usually a trace of albumin

SYMPTOMATOLOGY

The **incubation period** is usually 4 to 7 days In extreme cases it may be from 2 to 15 days

The **onset** is sudden the temperature rising rapidly to 103°F Although the temperature is very high, there is seldom a typical rigor There is severe headache and pains in the eyeballs with marked photophobia, pain in the back, in the bones, and all over the body, causing the patient to assume a characteristic stiff gait when walking and to toss from side to side in his bed The tongue is furred and red at the tip The face is flushed and the eyes are suffused There is very often general glandular enlargement

Other symptoms include constipation or a 'critical' diarrhœa accompanying the second rise of temperature

The **fever** varies considerably from case to case and from epidemic to epidemic, but there is a tendency for one type to predominate in each epidemic or seasonal exacerbation The seven days temperature is the classical form The temperature remains high for two or three days coming down slowly to about 99°, and then rises suddenly on the 6th or 7th day and drops to normal again

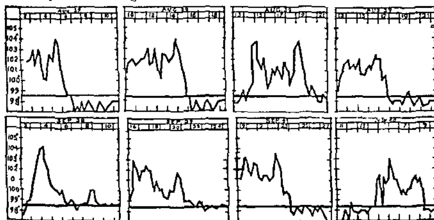


Figure 94 Showing temperature charts of six consecutive cases of dengue and two additional charts the last being a hospital infection

[illegible] a high remittent character Sometimes there is quite [illegible] rature before the final rise [illegible] two phase type of temperature chart

In milder epidemics there is only a single rise of temperature a sharp rise for two days which then fades away In this one phase or abortive type the second rise of temperature may be so slight that it is not noticed, or it may not occur at all

In exceptional cases, the second [illegible] is a three phase temperatu[illegible]

The **pulse** is usually [illegible] may fall before the tem[illegible] very low indeed, down to 40 per minute

Rashes —There are
at the onset is a transitor
and chest, and the secon ... about the fifth day or
even after the fall of temperature on the 7th or 8th day The latter is a macular or scarlatiniform rash, usually commencing on the hands and wrists or legs and extending to the chest, not usually to the face but otherwise all over the body It may be very irritating and in severe cases there is later marked desquamation

The
diarr
thoug ... not common They include acute depression amounting to definite melancholia, multiple joint pains, pain in one or two joints which may be very troublesome and last for two or three months or even longer, and a tendency to faint

Variations in the symptomatology —The different temperature charts that are encountered are discussed above, other symptoms especially the rashes, show
epidemic
in 10 per ce

... in others it never occurs

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis must be made on the clinical evidence and by a process of exclusion, there are no positive laboratory tests The short fevers that have to be excluded include sand fly fever (*vide infra*), malaria—definite rigor, periodicity, and the finding of parasites, influenza—catarrhal symptoms and absence of rash, measles
spots, scarlet fever—not common in
absence of rash and finding of the
(leptospiral) The more serious conc
of greater intensity with much albun
small pox, and typhus

The severe pains might simulate rheumatic fever, and the rash, which is sometimes very intense, secondary syphilis

PREVENTION

The only practical measure of dengue prevention is the control of aedes Aedes have a very limited flight, so that the elimination of their breeding places does not present very great difficulties if properly organized. Spray-killing of the adult mosquito should also be undertaken, in both day and night quarters Other measures should include screening and/or the use of mosquito nets, and the application of repellent substances to the ankles, wrists and other exposed parts of the body (*vide supra*, pp 119 and 305)

TREATMENT

There is no specific treatment

A salicylate mixture should be prescribed and a brisk purgative, for example, $\frac{1}{4}$-grain doses of calomel every half hour up to six doses followed by salts in the morning Aspirin may be given in addition for the pains, and bromides or phenobarbitone for the sleeplessness For persisting joint pains local analgesic ointments or liniments, such as oil of wintergreen should be applied, and a mixture containing tincture of belladonna and tincture of colchicum given

Prognosis —This is always good In extensive epidemics, the death rate has been placed at about 0 2 per cent, the deaths occurring amongst old and debilitated persons

SAND-FLY FEVER

Definition —Sand-fly or phlebotomus fever is a fever of short duration characterized by headache, pain in the eyeballs and all over the body, and often by great prostration It is caused by a filtrable virus which is transmitted from man to man by sand-flies

particularly in India It
'U O), climatic fever, and
separate entity In 1909
blood infection and that
he virus was filtrable and
Birt showed that sand-
Shortt and others (1934)
of the fever

EPIDEMIOLOGY

It has a wide geographical distribution in tropical and sub-tropical regions, but mainly in the latter, it occurs in the Mediterranean littoral including north Africa, Egypt and Palestine, in Syria, Iraq, Iran, north-west India, and central and south America

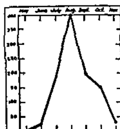


Figure 95 Seasonal distribution of sand fly fever in Palestine (Walker and Dods 1941)

It does not usually occur above 4,000 feet, and never above 7,000 feet

It usually occurs in late summer and autumn (*vide* figure 95), but the incidence curve will vary in different localities The sand-fly season in north-west India starts in April or May and lasts until October

ÆTIOLOGY

The virus —The virus is filtrable and passes through L_3 and L_5 Chamberland filters It circulates in the blood one day before and during the first two days of the attack

Monkeys can be infected

Transmission —It is transmitted by *Phlebotomus papatasii*, the golden-coloured sand-fly The virus undergoes a stage of development in the sand-fly, during which it is not transmissible Transmission will occur on the seventh day after the infecting feed, and the sand-fly remains infectious for the rest of its life The virus is said to be transmitted to the next generation, possibly the larvæ become infected by feeding on the bodies of dead adults

Immunity —It is generally considered that ...

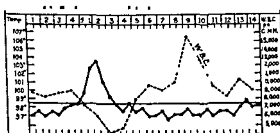


Figure 96 Temperature chart with leucocyte count records in sand-fly fever (Whittingham, 1938)

... change is an increase in the permeability of the blood tissue barrier especially of the blood-brain barrier, though apparently the virus does not pass the latter

The blood picture shows a sharp leucopenia associated with an absolute increase in immature granulocytes during the fever, often followed by a leucocytosis (*see* figure 96)

SYMPTOMATOLOGY

The **incubation period** is from 4 to 10 days, usually about 6 days The **onset** occurs with chill The average duration of the **fever** is 3 to 4 days, but it may be longer A secondary rise is comparatively rare The **pulse** is strikingly slow, often from the second day of the fever

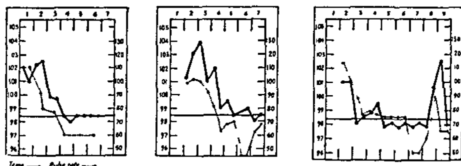


Figure 97 Three sand fly fever temperature charts, the first two are typical, and the last is unusual and shows a terminal rise suggestive of dengue (Walker and Dods *loc cit*)

There is a general puffiness, and uniform flushing of the face, the con-

prostra-
amed by
late, but
much the
pain on
There
round

There may be general hyperæsthesia of the skin of the face, head and trunk, and absence of the biceps and supinator reflexes

Papillœdema has recently been reported as constantly present in this disease in a severe epidemic in British soldiers (Shee, 1942)

Complications —There are not very many complications, but a condition suggesting benign lymphocytic meningitis has been reported

Diagnosis and differential diagnosis —This is clinical and by a process of exclusion The disease has to be distinguished mainly from malaria, dengue and influenza, the complete absence of catarrhal symptoms helps in the last named The author has seen a case diagnosed as small-pox, the sand fly bites on the forehead and wrists providing the characteristic shotty feeling

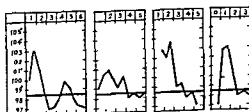


Figure 98 Sand fly fever temperature charts from Peshawar (Anderson 1941)

The muscular pains and more especially the band-like pain around the lower part of the thoracic cage suggest Bornholm disease Sand fly fever can be distinguished from benign lymphocytic meningitis, which it may simulate, by the low lymphocyte count in the cerebrospinal fluid in the former

PREVENTION

Preventive measures are all aimed at the sand-fly They can be summarized as follows —

(a) The avoidance of localities that are heavily infested with sand flies or from the nature of the terrain likely to be so infested at the favourable season
(b) The elimination or treatment of their breeding places
(c) The elimination or treatment of the resting places of the adult fly
(d) Personal preventive measures against the bites of sand-flies

(a) Much can be done by the proper choice of a camping ground especially by the avoidance of a 'cool' river bank, moving a bed or tent even a hundred yards may make all the difference Top floors are preferable to ground floors, and open airy rooms to shut-in ones

(b) The sand-fly requires, for its breeding place, darkness and protection from air currents, a comparatively even 'effective' temperature, moisture which also helps to maintain this temperature, and food in the

vegetable matter

that it is only necessary to control the
round the house or camp, a provisional
pted for this They breed in heaps of
ited buildings in the banks of rivers,
streams, or ditches, in the internal or external cracks in any form of building, in disused fireplaces and chimneys, and even in the cracks in the dried earth

Inhabited buildings should therefore be kept in repair and all cracks filled up before the sand-fly season Where this is not possible for any reason, they can be treated with a mixture consisting of 10 per cent of naphthalene dissolved in kerosene—four pounds of naphthalene balls added to a 4 gallon drum of kerosene and allowed to dissolve for three days

(c) Resting places for the adult flies should be reduced to a minimum by removal of curtains pictures, superfluous furniture, and collections of clothes, and the elimination of all dark corners Rooms should be fumigated or sprayed with any suitable anti-malarial fumigant or spray

he fumigation
Closed drains

sufficiently fine
mesh to keep out sand-flies—for this purpose the nets must be 45/46 mesh (*vide* p 119), or electric fans where these are available, the wearing of suitable protective clothing in the evenings, protection of the ankles by means of mosquito boots, and the application of repellent creams to the ankles and exposed parts of the body (*vide* pp 118 and 119)

Treatment.—This is mainly symptomatic Aspirin phenacetin and caffeine, or phenobarbitone in more severe cases, should be given for the pains and headaches Dover's powder is useful, and Manson-Bahr considers that opium is a specific, recommending doses of 30 minims of the tincture

Prognosis is uniformly good

COMPARABLE FEATURES OF DENGUE AND SAND FLY FEVER

Common.—They are short fevers with many common clinical features, are caused by filtrable viruses, and are transmitted by insects The virus is present in the patient's blood for 3 days and takes about a week to develop in the insect

Distinguishing.—These can be best shown in the form of a tabular statement :—

SYMPTOMATOLOGY

The **incubation period** is from 4 to 10 days, usually about 6 days The **onset** occurs with chill The average duration of the **fever** is 3 to 4 days, but it may be longer A secondary rise is comparatively rare The **pulse** is strikingly slow, often from the second day of the fever

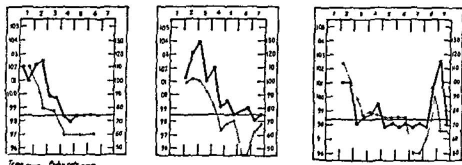


Figure 97 Three sand fly fever temperature charts the first two are typical, and the last is unusual and shows a terminal rise suggestive of dengue (Walker and Dods *loc cit*)

There s a general n ffness and n f ... the con- ... prostra- ... anied by ... late but the fauces are congested Th ... much the same as in dengue, but hea ... pain on movement of the eyeballs ... There is in some epidemics a sensation of an intense band-like restriction round the liver region, which suggests hepatitis, or severe hepatic congestion

A rash is exceptional

There may be general hyperæsthesia of the skin of the face, head and trunk, and absence of the biceps and supinator reflexes

Papillœdema has recently been reported as constantly present in this disease in a severe epidemic in British soldiers (Shee 1942)

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Figure 98 Sand fly fever temperature charts from Peshawar (Anderson 1941)

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(c) The elimination or treatment of the resting places of the adult fly
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(b) The sand-fly requires, for its breeding place, darkness and protection from air currents, a comparatively even 'effective' temperature, moisture which also helps to maintain this temperature, and food in the form [illegible] able matter

It [illegible] it is only necessary to control the [illegible] se or camp, a provisional [illegible] They breed in heaps of [illegible] in the banks of rivers, [illegible] l cracks in any form of [illegible] even in the cracks in the [illegible] earth

Inhabited buildings should therefore be kept in repair and all cracks filled up before the sand-fly season Where this is not possible for any reason, they can be treated with a mixture consisting of 10 per cent of naphthalene dissolved in kerosene—four pounds of naphthalene balls added to a 4-gallon drum of kerosene and allowed to dissolve for three days

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Common.—They are short fevers with many common clinical features, are caused by filtrable viruses, and are transmitted by insects The virus is present in the patient's blood for 3 days and takes about a week to develop in the insect

Distinguishing.—These can be best shown in the form of a tabular statement :—

	Dengue	Sand-fly fever
1	Virus present for first 3 days of fever	Virus present day before fever and for the first 2 days after onset
2	Transmitted by *Aedes aegypti*	Transmitted by *Phlebotomus papatasii*
3	Eight days' development in mosquito	Seven days' development in sand fly
4	Mainly tropical	Mainly sub-tropical
5	Fever lasts 5 to 7 days usually, sometimes less	Fever lasts 3 to 4 days usually, sometimes longer
	Secondary rise of temperature occurs in 25 to 80 per cent of cases in different epidemics	Rare
6	Primary rash occasionally, secondary rash all over the body, in most epidemics	Rare
7	Immunity is variable and tends to be short	Immunity is usually complete

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Addendum.—Several outbreaks of short fever of unknown ætiology have been [illegible]
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tly develops epi
sm is the plague
severe epizootic
nitted to man by
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all the rubbish to be collected and as
appeased and the disease disappeared

Plague was described by various writers in the classical period as occurring in the countries around the eastern Mediterranean The Justinian pandemic of 543 A.D is said to have reached Europe from Egypt and spread throughout the Roman Empire along the lines of human communication The greatest European epidemic however, was the Black Death starting in *1346 A.D It is reported* to have reached Europe from the near east it spread all over Europe and

adjacent countries, and killed, we are told, one-quarter of the population of the then-known world References to this great outbreak occur in the histories of many countries Another European epidemic occurred in the ten years following 1664 and in London about one-sixth of the population is said to have died in the first two years These were only the great visitations of plague, and actually plague was never absent from Europe between the 14th century and the beginning of the 19th century, in the years between the great pestilences many minor outbreaks occurred

The third great pandemic of the present millenium started in 1894 and is now apparently drawing to its close It originated in Yunan province in China and rapidly spread to Hong-Kong, Japan and the Philippine Islands In 1896 it appeared in Bombay which had been free from plague for nearly two hundred years and thence it spread over most of India From India it spread to Africa and to Australasia (1899), Hawaii Central and South America (1899), to the United States (San Francisco, 1900), and to a limited extent to Europe This pandemic involved almost the whole world, India, however, suffered most In some of the early years of this century the deaths from plague in India numbered over a million, and in 1907 they reached a peak of nearly 1½ millions, since when they have steadily declined

In the United States, on the other hand, from the time of the first introduction of the disease in 1900 to 1941, only 501 cases with 316 deaths have been reported These cases have occurred in eight states, the first appearance of the disease was as follows —California 1900, Washington 1907 Louisiana, 1914, Florida 1920 Texas 1920, Oregon 1934 Utah 1936 and Nevada 1937 Up to January 1942 the last two human cases reported occurred in Siskiyou County, California, in June 1941

EPIDEMIOLOGY

Geographical distribution —Plague is now endemic in India, B[illegible], Ceylon, Java, China, and Mad[illegible]

[illegible]

sec



Figure 99 World pla[illegible]
A [illegible]
B [illegible]
C [illegible]
[illegible]

In China, it is now mainly confined to western Shansi province where the Yellow River flows between this and Shensi province, in which some foci of infection are also present, to Fukien province where in the mountainous areas pneumonic plague also occurs, and to Manchuria In the first two areas the rat is the main reservoir, whereas in Manchuria other rodents, the marmot or tarabagan, are responsible and the disease is more sporadic, but is very liable to develop into a pneumonic epidemic

I . . ery liable to develop into a pneumonic epidemic ll endemic in the Bombay Presidency, in Hyderabad l new in Bihar, the United Provinces northern India In Bengal years, and in the eastern and

and in a it and Assam, no plague has occu southern parts of Madras it is comparatively rare

Epidemic features —Recent studies in plague have shown that there are two main epidemiological groups, (a) urban and domestic plague and (b) selvatic plague, and that in each of these epidemiological groups the disease may develop from the bubonic to the pneumonic form, when its epidemiology will undergo a corresponding change

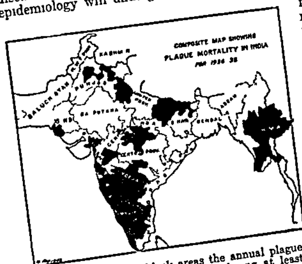


Figure 100 In the black areas the annual plague mortality was over 0 1 per mille during at least one of these years

The urban and domestic form (transmitted from rats) occurs in densely populated areas and spreads along trade routes and overseas in ships It is primarily bubonic and sporadic, but bubonic plague may assume epidemic proportions and spread like an epidemic disease, though, as will be shown below, it is not a truly epidemic disease*

In certain circumstances probably connected mainly with the atmospheric temperature as it occurs mo frequently in cold coun tries, pneumonic form appear and the disea takes on a truly epidem form, being transmitted directly from man to man

---

* The author is aware that here he is endowing the word *epidemic* with a spe meaning that it does not always convey The *Oxford Dictionary* quoting from *Sydenham Society Lexicon* gives the meaning as 'Prevalent among a people community at a special time, and produced by some special causes not gene present in the affected locality' This admittedly allows a wider meaning but if goes back a little further to its earliest use (according to the *Oxford Dictio* one finds a more restricted meaning Bacon (1622) It was conceived not to b epidemick disease but to proceed from a malignity in the constitution of the

Language is a living thing and it must be continually growing and cha Bacon's conception of an 'epidemick' disease as being possibly a divine punishm curse or a spell *upon the people* entirely independent of environment, could upheld and the Sydenham Society gave the word a wider meaning To-da knowledge about epidemic disease is more precise but the word *epidemic* has precision, its meaning certainly goes far beyond that given to it by the Syd Society for we have epidemics of malaria in countries where the disease has o continuously for a thousand years We must therefore invent a new word or nd restrict the meaning of the old one

Selvatic plague (transmitted from wild rodents) that occurs in rural areas and amongst workers in the woods and fields is primarily a sporadic, bubonic plague, but is even more apt to develop into the pneumonic form, when it may be the starting point of a serious pneumonic epidemic (e g the Manchurian epidemics of 1910–11 and 1920–21 in which there were about 50,000 and 10,000 deaths, respectively)

Seasonal and year to year incidence.—Temperature and humidity have a marked influence on the spread of plague A moderate temperature, 60°F , and

deficiency c

at 70°F , o

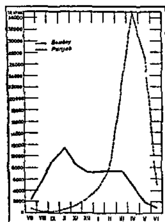


Figure 101 Monthly plague incidence, 1898–1931

As well as the periodic epidemic-like waves of plague, in the production of which many factors are involved, there are in the endemic areas from year to year considerable variations in the incidence, which are associated with climatic variations, and Rogers (1933) has shown that, by studying the past meteorological data, it is possible to forecast whether it will be a good or bad plague year, long spells of abnormally hot and dry weather tend to reduce the incidence during the next plague season, and *vice versa*

Age, sex and race incidence —In the urban and domestic bubonic form, persons of all ages and both sexes are equally susceptible and there does not seem to be any racial immunity In the pneumonic form, adults, both men and women, who attend the sick, and in the sporadic selvatic form, men, who are more likely to come in contact with the sources of infection, are most frequently attacked

---

The definition of an epidemic (*trans* upon the people) that the writer has adopted for his own use is 'an outbreak of a disease that is transmitted *from man to man*, directly or indirectly but in the transmission of which *man forms an essential link*'

Application of this restriction on the meaning of the word *epidemic* does not entail interference with established nomenclature of disease since diseases to which the word *epidemic* is regularly attached in a defining sense e.g epidemic typhus, are epidemic diseases in the restricted sense and so-called epidemic dropsy' is a misnomer already overdue for renaming, which is only awaiting a definite decision regarding its ætiology

It would be rational to define *endemic* (*trans* in or amongst the people) on the same lines, and to use the word *sporadic* when the disease did not comply with the restriction that 'man forms an essential link' But the word *endemic* is already so deeply involved in disease nomenclature, e g., 'endemic typhus' which is not an endemic but essentially a sporadic disease, according to the suggested definition, that it will be difficult to drop it

All these epidemiological observations are explainable on the grounds of the known ætiology of the disease which is discussed below

ÆTIOLOGY

Historical — The [illegible]
who [illegible]
T [illegible]
is a sm[illegible]
pleomo[illegible]
polar staining

Culture —It is an aerobe and a facultative anaerobe It grows easily on ordinary culture medium producing very small round colourless transparent granular colonies in 24 hours at 37°C, increasing to large (4 mm) [illegible] a flaky [illegible]ated on the surface, 'stalactites' grow down from the under-surface of the oil globule

There is no hæmolysis on blood agar

Resistance —These organisms are killed by drying at room temperature in a day or two, by heat at 55°C in 5 minutes, and by 0 5 per cent phenol in 15 minutes They survive in the cold almost indefinitely

Distribution in the body and routes of escape —Plague bacilli invade the skin causing vesicular or pustular lesions, the local lymphatic system, causing buboes, and the blood stream, in this order, the infection does not however reach and persist in the blood in every case, but when it does the bacilli can naturally be found in every organ in the body Under certain conditions, the lungs become the site of an intensive infection

In the ordinary septicæmic infection the bacilli do not escape from the body in any of the normal secretions or excretions, but in the pneumonic form they escape in droplets during forced expiration

Susceptible animals —Man and both laboratory and wild rodents, and also monkeys are very susceptible, dogs, cats, cattle, sheep, goats and horses are difficult to infect, but most birds are immune

Toxins —No true exotoxin is formed, but bacillary filtrates cause severe toxic reactions and immune serum can be prepared by injecting animals (horses) with killed or living cultures

Transmission

Historical —In the historical records of plague epidemics in many countries, it was noted that rats began to die before human beings were affected and the outbreaks in rats and in man were regarded as being intimately connected The early investigators at the end of the last century failed to follow up this obvious lead and the first Indian Plague Commission (1901) went so far as to state categorically that there was no evidence that the disease was carried by infected rats in ships In 1897, however Ogata suggested tentatively that the flea might play a part in transmission and in 1898 Simond working in Bombay enunciated the main facts about the transmission epidemiology and control of plague which have remained practically unmodified, to the present day

Lowe (1942) summarizes Simond's contribution to the transmission problem as follows —

'He stated that the introduction of plague rats into a healthy area was generally followed by an epidemic of plague in man but that introduction of an infected man into a healthy area was often not followed by an epidemic. He found that the epizootic preceded the epidemic that it was usually localized in one area of a town to begin with, and that human plague later started in that particular area

He noticed that in about 5 per cent of human cases a primary lesion in the form of a blister containing plague bacilli was seen, and recorded the site in the body of many of these blisters and found that they were most common on the

foot and leg He considered that the blister was probably at the site of the bite of the transmitting insect (This is the only observation for which he is usually given credit)

nd that a plague
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considered that the mode of transmission of plague was from rat to rat and rat
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suggested
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disappear-
population
to migration of others and to a high degree of immunity of the remaining rats and thought that repopulation of the area by new strains of susceptible rats might cause recrudescence He also believed that plague might continue to linger among rats in a benign form in the period following an epidemic and that sporadic cases in man might thus be explained

He stated that t
of rats and also of
human habitations
conveyance of plag
by the destruction
advocated the use c

Gauthier and Raybaud (1902) narrowed down the issue and transmitted plague from rat to rat by means of the bite of fleas

Simond's work was confirmed by the Plague Investigation Commission (1904 to 1913) these workers amplified Simond's work but added little of basic importance to it

The *primary* transmission cycle of infection is rat–flea–rat The flea becomes infected from the blood of an infected rat, and transmits the infection to another rat by its 'bite There are a number of other rodents that are capable of playing the part of the rat in the transmission cycle

The infection of man is an off-shoot from this primary cycle, and normally, from the bacillus's point of view man constitutes a *cul-de sac* Man is capable of constituting a link but as only very rarely are bacilli present in human blood in sufficiently large numbers to infect fleas that ingest his blood, and, as the fleas that normally infest man *e g Pulex irritans* are not good transmitters of plague bacilli man constitutes a very weak link in the mammal–flea–mammal cycle of bubonic plague trans mission Bubonic plague is thus never truly epidemic though the disease may assume epidem

In certain circ climatic conditions or other alized in the lungs and produce a pneumonia when this has once occurred the

Infection may also take place via the alimentary tract e g in Manchuria infection has been caused by the eating of under cooked

epidemiology of the disease

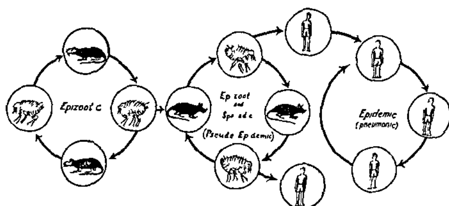


Figure 102 The transmission cycles in plague infection
Left hand cycle Brown rat—flea epizootic cycle
Middle cycle Black rat—flea epizootic cycle from which man is infected sporadically
Right hand cycle Man to man epidemic cycle of pneumonic plague

Infection has been acquired at a post mortem examination and in the laboratory

Finally, the bacillus has been injected with homicidal intent such an instance occurred in Calcutta in 1933 when two accused including one doctor were convicted of murder

Essentials for transmission of bubonic plague

The four essentials for the transmission of bubonic plague are thus —

1 *The plague bacillus*
2 *The rat or other rodent—the natural host and reservoir of infection.*
3 *The rat flea or other flea vector*
4

Giv

variation

(of 2 and 3) susceptibility (mainly of 2 and 3) and environment and habits (of 2 3 and 4)

as far as present day know with regard ally be where marmot,

pneumonic cases with 31 deaths the reservo

squirrel but even here the epidemic occurred in mid winter

2 *The rodent* Species —There are two main groups of rodents involved in plague transmission (i) rats which in a general way, live in *close association with man*—though some species live in closer association than others—and are the rodents responsible for the epidemic like

(ii) wild

n plague
ge brown
(grey) sewer rat, *Rattus norvegicus* Rats of other genera, *Gunomys* and bandicoots, are also susceptible, but from their habits are a less important menace to man

(ii) The tarabagan or marmot (*Arctomys bobac*) and several species *Citellus* (Susliks) in the Caucasus Siberia and Manchuria, the jerboa in southern Russia, the gerbille and the multimammate mouse, *Mastomyx coucha*, in Africa, and the ground squirrel (*Citellus beecheyi*) in California, are the most important reservoirs of selvatic plague

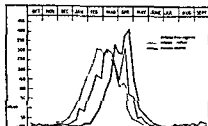
The rat-factors determining incidence these are—

experience of the rat population

(b) *Habits* the reservoir of infection must come into close association with man, by natural inclination and/or by opportunity This factor will depend on the species again, and on the environment

(c) *Density of the rat population*, the disease will not assume epidemic proportions unless there is a sufficient number of susceptible rats living in close contact with man The rat index calculated from the number of rats caught in a given time in one hundred standard traps must be at least 50 The rat index will depend on environment and food supply

The development of conditions for an outbreak of plague in man — The usual sequence of events is as follows —The grey rat, which infests docks and generally from his habits makes more contacts with the outside world is the first to become infected one such rat acquires plague and dies, its fleas leave the dead body and parasitize other rats to whom they transmit the infection, and so a *grey rat epizootic* develops In time a certain number of fleas from the plague-infected grey rats infest the more venturesome amongst the black rats and the *epizootic spreads to the domestic rat population* Infected fleas are thus brought into man's habitations, and when the rat population becomes reduced the fleas from a dead rat failing to find another rat begin to infest man and when this incident is repeated many times an outbreak, which assumes *epidemic proportions*, occurs amongst the human population (*see* figure 103)



In course of time a point arrives when the whole rat population has been infected a large number have died and the rest have recovered and are immune, so that the epizootic and the human outbreak come to an end Epizootic conditions cannot arise again until a new generation of non immune rats grows up However, over a

to be by a process of elimination of the more susceptible members of the community.

Unless there is a considerable population of *R rattus*, plague is never transmitted to man *to any serious extent, and it is suggested that the* replacement of the *R rattus* population by *R norvegicus* in many European countries, which started in the 17th century, accounts for the failure of plague to establish itself in these *countries during the last two* centuries, though it has been widespread in other countries where *R rattus* still abounds Again, in Bengal the predominant rat is not *R rattus* (13 per cent), but *Gunomys varius* (28 per cent) and the bandicoot that are not so susceptible to plague, nor do they live inside houses, consequently plague is rare

Another theory regarding the relative immunity of the Bengal rats to plague infection is that they have in the recent past suffered another pasteurella epizoötic which was less fatal than *Past pestis,* and that this pasteurella has in its antigenic structure some elements common with *Past pestis*

The most effective method of control of plague is by reducing the rat ... reported ... y, where ... ipply are ... ow, and, conversely, *where houses* are mainly constructed of wood or some other soft material and where domestic garbage is thrown out without regard to sanitary and domestic tidiness, as in many Indian towns and villages, ... *tage is set for the type* ... years of the present ... Inited States, p 323) ... station, not to sanitary ... large tracts of country ... rats burrowing deeply into the ground, as well as to the ... competitors for garbage, some of which are the rat's natural enemies, *e g* crows, cats, jackals, and pariah dogs, which abound in all towns in Bengal

In Manchuria, where the marmot is the wild rodent concerned this rodent is not killed by plague infection, and, though it may infect a large number of fleas, it does not die, and the *fleas* do not leave it, so that by this means the infection does not spread rapidly and acquire *epidemic proportions,* but remains endemic Further, this rodent does not normally *come into* close association with man However, sporadic infections thus acquired are apt to be grave ones and frequently develop into pneumonic plague, and as such may be passed rapidly from man to man and constitute an epidemic

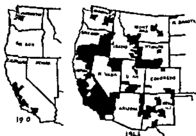


Figure 104 Showing extension of known areas of plague infection in the western states of the U S A

A third set of conditions exists in California where the ground squirrel suffers epizoötic visitations of plague, yet little human plague has occurred, there have only been 8 cases in the *last 10 years** *The danger here is*

* Later ... 1943 one human case of plague was reported from Siskiyou County California ... pools of fleas collected on rodents ... ana (9) New Mexic ... *th Rep* 1944 *59,* 91 ... 1944

that fleas from these squirrels should be taken into the houses by other rodents which are themselves perhaps not susceptible or by domestic animals or that an epizootic should arise amongst rodents that do frequent human inhabitations For these reasons large sums of money have been spent on rodent destruction in that country

The infection in the flea s gut al o passes forwards and eventually a ma sive infection may block the pharynx of the flea When the flea attempts to take another blood meal the blood will not pass this plug of bacilli which have to be ejected by a regurgitatory effort and the bacilli are thus injected via the flea s proboscis into the new host A third method by which the flea transmits the infection is by contamination of its mandibles whil t feeding on an infected host and direct transference of the *materies morbi* to another host Of these three methods the second is almost certainly the most important

Only a comparatively small percentage of fleas feeding on an infected rat will become infected and of those that become infected only a small percentage will transmit the infection the percentages vary according to circumstances

The flea factors determining incidence these are—

(*a*) *Efficiency of the flea as a transmitter* which will vary according to (i) species and (ii) environmental (climatic) conditions under which it lives

(*b*) *Longevity of the flea and maintenance of infection* which is again

(*d*) *Density of flea population* which will depend on the climate and the rat population varying directly with the latter this is measured by a flea index which gives the average number of fleas on each trapped rat a cheopis index of at least 3 appears to be necessary for epizootic conditions

(i) Species —The most important transmitter of rat borne plague in the tropics is *Xenopsylla cheopis* Another rat flea *Xenopsylla astia* also common in the tropics is capable of transmitting plague but is a relatively poor transmitter and

reaches epidemic proportions

long so that in endemic areas

season Another relatively pc

(The low incidence of plague

index *X astia* being the common flea)

In temperate countries *Nosopsyllus fasciatus* and *Leptopsylla segni* are the important transmitters

Pulex irritans the flea that commonly infests man is capable of transmitting the infection (*vide supra*) as are many other fleas such as the do and the cat fleas *Ctenocephalus canis* and *Ctenocephalus felis*

The other rodent carriers have their various fleas most of which wil in special circumstances bite man and are capable of transmitting plague

For example, *Ceratophyllus tesquorum*, of the marmot will show the 'blocking' phenomenon, if fe... and *Xenopsylla eridos* of the... *Diamanus montanus* of the (mitters

(ii) Environmental (climatic) conditions —These have a marked effect on the flea *X cheopis* breeds best at a temperature between 68°F and 77°F, and in the presence of a high degree of humidity Above 85°F not only does breeding slow down, but this high temperature adversely affects plague-infected fleas, so that as the temperature rises, transmission decreases and eventually ceases Humidity is also an important factor, and in the tropics a saturation deficiency of less than 10 millibars is necessary for effective transmission under dry conditions 'blocked' fleas rapidly die Thus, l... inimics... ence... portant one, and it has been shown that in deep rat burrows, temperature and humidity may remain suitable for flea survival and transmission of infection long after the surface atmosphere has become quite inimical to both It is believed that it is by this means that infection survives the hot dry season in some places (George and Webster 1934) Conversely, in cold countries fleas may find micro climates, *e g* in houses and in ships, which are warm enough for them

Where other fleas are the transmitters, the ranges of temperature and humidity idea... transmission may be different but

4 *Man* ... le evidence of any differences in ... is

The *density of the human population will of course influence the actual* number of cases in a particular area, but overcrowding will only lead to an arithmetical and not a geometrical increase as would be the case in ... ote, p 324) As however, overcrowding ...y conditions in which rats are likely to ... transmission If man's environment is ... food for rats and to encourage a clo e association between rats and man the conditions will be favourable for a ... be introduced ... maximal when the infection is intro- ... are most favourable that is where *R rattus* is the predominant rat and is abundant where *X cheopis* is the

Spread of infection outside endemic areas

...ation *per se* play ... be carried by s... *egicus* is a more ready traveller ... distances

The ability of the flea to survive in grain bags, gunnies etc, for long periods even under unfavourable external atmospheric conditions, has only recently been fully appreciated and it is believed that this mode of

transfer of infected fleas plays an important part in carrying infection from place to place

PATHOLOGY

General reaction to infection—There are three lines of defence against the invading bacillus (a) the skin, (b) the lymphatic glands, and (c) the humoral antibodies in the blood If the bacilli are held up at the first

vesicle
eaction
bacilli
second

line of defence, namely the first group of lymphatic glands to which the lymphatic vessels pass the glands will be enlarged If the bacilli pass the second line they reach the blood stream in small numbers at first, and are distributed widely in the body where, exercising their affinity for lymphatic glands, they affect these mainly causing a general adenitis, the infection may be overcome by the humoral antibodies in the blood and the bacilli will reappear in the blood only as temporary showers If, on the other hand, they overcome the humoral antibodies in the blood, they will cause a septicæmia

The invasion of the lung parenchyma is also probably a matter of local resistance, as well as of some natural or acquired intrinsic quality in the bacilli themselves, but this appears to the writer to be an incident outside the natural sequence of invasion

The local lesions are the clinical manifestations of an acute inflammatory reaction, and a rapid passage of the defences indicates a failure of the local resistance Hence, the local vesicle or pustule is more commonly seen in ambulant cases or in cases of pestis minor, and clinical buboes are usually absent in the severe septicæmic cases, though at post-mortem examination the glands will be found slightly enlarged

Morbid anatomy.—There is usually a post-mortem rise of temperature and early decomposition there may be ecchymoses all over the body and submucous hæmorrhages

The plague toxin has a particular affinity for the endothelial cells of arterioles and lymphatics, in these, it causes degenerative changes which lead to extravasation of blood into the tissues All the organs are congested and there are numerous hæmorrhages in the solid viscera into the lumina of the hollow viscera, and into serous cavities

In bubonic and septicæmic plague the lymphatic glands are enlarged, red and congested, and surrounded by a hæmorrhagic œdema Histological sections show a hyperplasia, invasion by large numbers of bacilli which are multiplying, small necrotic areas into which hæmorrhage has taken place, and often small abscesses The spleen is enlarged it is congested

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pericardial effusion

In pneumonic cases, there is a hæmorrhagic pleurisy, and the alveoli are filled with a hæmorrhagic exudate The inflammatory condition extends to the bronchioles the bronchi and even the larynx and trachea, and the bronchial lymphatic glands are involved It is usually a central pneumonia

The blood picture—There is never any anæmia except in the chronic suppurative stages of the infection, on the contrary, the great dehydration in the early stages may lead to polycythæmia A leucocytosis is almost invariable except in the very severe pneumonic cases when paradoxically it may be absent The count often rises to 20 to 25 thousand leucocytes per c mm, or even higher, with an increase in the percentage of lymphocytes and a decrease in large mononuclears, at first, but later there may be a relative as well as an actual granulocytosis

In severe septicæmic cases, bacilli may be present in the blood in sufficiently large numbers to make it possible to find them in an ordinary blood smear

The urine—This is scanty and highly coloured It usually contains an appreciable amount of albumin, except in very mild cases The urea, uric acid and chloride excretion are reduced A few red blood cells are commonly seen, and there may be obvious hæmaturia

Suppression of urine may occur in severe cases, when there is much dehydration and a low blood pressure

SYMPTOMATOLOGY

Clinical types—These have been foreshadowed in the preceding paragraphs, there are five main clinical types —

(i) *The ambulant* in which there is only a vesicle at the site of invasion with a little local lymphangitis and no constitutional symptoms

(ii) *Pestis minor*, in which there is a single gland or a single group affected and only mild constitutional symptoms

(iii) *Bubonic plague* in which the local group of glands mainly but also other glands in different parts of the body are affected and there are usually grave constitutional symptoms

(iv) *Septicæmic plague* in which there is an established virulent septicæmia and usually a rapidly fatal course

(v) *Pneumonic plague*

The so called cellulo cutaneous type which is now relatively rare but from historical records appears to have at one time been the common form may occur in either the bubonic type in which the local cellulo cutaneous lesion corresponds to the bubo, or in the septicæmic type, it is probably more common in the latter

It should perhaps be emphasized that there is no sharp line of distinction between the bubonic and the septicæmic types, if there is a general adenitis, there must at some time have been a bacillary shower in the blood In the severe bubonic type, these showers are probably repeated frequently, it is only when the bacillary invasion overcomes, though perhaps only temporarily, the humoral antibodies in the blood that a septicæmia is established

The first two types need no further description

Bubonic and Septicæmic Plague

The incubation period is from two to eight days, rarely longer, the average is about four days

There are sometimes **prodromal symptoms** for a day or two with malaise, anorexia, apathy, headache and possibly aching pains in the groin, or elsewhere at the site of the subsequent buboes Usually however the **onset** is sudden, with a rigor and a temperature rising to

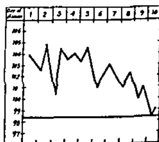


Figure 105 Temperature chart in a case of bubonic plague

103° or higher in the first 24 hours, the pulse is rapid and the respirations are increased There is a severe frontal headache, the mental state is confused, and the speech slurred, there are tremors of the tongue and

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... The urine is scanty

The temperature

to excitement and

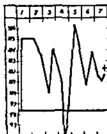


Figure 106 Temperature chart in a fatal case of septicæmic plague

death, but it does occur in non-fatal cases In the more favourable cases, the temperature comes down gradually, reaching normal within five or six days The fall of temperature is usually synchronous with

usually be felt, but death follows before any further development takes place In the bubonic case, they develop rapidly, they are red, swollen and tender, the discrete glands cannot be felt, as they are matted and surrounded by œdematous cellular tissue They are very painful and the patient lies with his knees flexed and/or arms extended to relieve the pressure

The site of the invasion determines which are the main glands affected, the bare-footed Indian is usually bitten on the toe, so that in India 70 per

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supra)

In bubonic cases the glands eventually suppurate, and may become secondarily infected

In septicæmic plague, the lymphatic glands are only slightly enlarged in the fatal cases, but, if the patient recovers, or if death is postponed beyond the usual four or five days, some enlargement ...

an indolent ulcer forms

bubo

burst

and cause profuse and fatal hæmorrhage When they do burst, they may form chronic sinuses which become secondarily infected, and the patient may die some weeks later from sepsis, exhaustion, or amyloid disease Or chronic ulcers may form

Another complication is septic pneumonia, which will often develop in a debilitated patient with open sinuses, this condition should not be confused with pneumonic plague

Pneumonic Plague

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watery sp

eventually develops the classical 'prune-juice' colour and consistency The patient has an anxious expression There is not usually much pain in the chest but the patient is cyanotic and some dyspnœa develops early The physical signs are not characteristic of pneumonia, there is little

the vocal resonance is unchanged but

ls to the right of the sternum and the

od pressure is low The pulse rate

becomes

nes uncountable Death

and it is seldom deferred

the form of submucous hæmorrhages purpuric spots epistaxis hæmoptysis hæmatemesis, hæmaturia and/or melæna

DIAGNOSIS

Clinical—A typical case of severe bubonic or septicæmic plague presents a characteristic picture the sudden onset high temperature rapid pulse, great prostration bloated appearance and conjunctival suffusion the slurred speech and staggering gait the apathy and mental confusion and eventually the buboes in the former, are not likely to be confused with any other condition except possibly typhus if the buboes are late in developing

Bacteriol

direct examination c

ulation

From the primary vesicle of the **ambulant** case or the bubo of **pestis minor**, material can be obtained by gland puncture in the latter case for direct examination or culture animal inoculation will usually be unnecessary as the organism will in most instances be uncontaminated by other organisms In the early stages of **bubonic plague** the same remark applies but later when the glands suppurate it will often be necessary to resort to animal inoculation to confirm the diagnosis

In **septicæmic plague**—and it must be remembered that all bubonic cases are potentially septicæmic—the organism can be obtained from the blood rarely by direct examination but always by culture and animal inoculation

In **pneumonic plague** the plague bacilli are present in large numbers in the sputum they can be recognized in a direct smear but it will be advisable to confirm the finding by animal inoculation whenever possible, as culture will be more difficult on account of contamination

Outline of technique—(i) *Smears* should be stained with Gram's stain and methylene or thionin blue *Pasteurella pestis* is gram negative and the characteristic bi polar staining will be easily recognized but confirmation of the identity of the organism should always be obtained if possible this is essential where one is dealing with an isolated case

(ii) To obtain a *culture*, inoculate blood sugar plates (pH 6.8 to 7.2) and broth tubes with gland juice Blood from the finger may be inoculated directly on to a plate or 5 c cm from a vein into 100 c cm broth flask The broth and plates should be kept at 22°C or at room temperature except in very hot or

cold climates On the plate delicate translucent dew-drop colonies appear, these are sticky and can be pushed along the surface of the plate The broth should show a pure growth

The certain identification of the culture is complicated by the fact that the plague bacillus is difficult to emulsify so that serological identification is almost impossible Animal inoculation is usually considered essential

(iii) For animal inoculation it is best to use two white rats and two guinea-pigs Some of the material should be inoculated subcutaneously into the groin and some rubbed into a shaved area on the abdomen of one of each species The latter procedure is important because if the material is inoculated subcutaneously the contaminating organisms may kill the animal before the plague infection develops In a positive case the animals will die of plague septicæmia within 3 to 5 days (Animals must be kept in insect proof cages during these tests)

The animal dying of plague will show general subcutaneous congestion and a fibrinous exudate in the peritoneum and locally necrosis of the tissues hæmorrhagic œdema, and the lymphatic glands enlarged and buried in hæmorrhagic œdema At the site of the percutaneous inoculation *i.e* the shaved area there may be umbilicated pustules In the guinea pig miliary necrotic nodules will be seen on the surface and throughout all the organs Pure cultures of plague bacilli will be obtainable from most of these sites

For the identification of the cultures of *Pasteurella pestis* 0 1 c cm of a 24 hour broth culture should be inoculated intraperitoneally the animal will die in two or three days

The agglutination test —This test is of no value in the diagnosis of plague for the reason stated above namely the difficulty of obtaining a

here

As mentioned above a septicæmic or a severe attack before the buboes develop may be mistaken for typhus and of course any other severe toxæmic condition, the typhus rash should be looked for, but it appears too late to be of any real value

PREVENTION

Prevention has to be considered under two main headings —

(*A*) *The prevention of the introduction of plague into a non-endemic area*

(*B*) *The control of plague in an endemic area*

The reader is referred back to p 328 where the transmission cycle is discussed

A The prevention of the introduction of plague into a non endemic

endemic
but how
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a and on

other factors For example, it will always be worth controlling the rats in dock areas in any country, but on the other hand prophylactic inoculation of the population where plague has not yet occurred would be a waste of energy

have to be made

B The control of plague in an endemic area.—If this cycle can be broken at any point, plague will not occur, if it can be weakened, plague will be reduced

In pneumonic plague the infection is passed from man to man (*see* figure 102, p 328, right-hand cycle), isolation of the sick is therefore essential to protect the general population, doctors, attendants, and nurses must be protected from droplet infection by masks and other measures. and the community as a whole should be protected against the effects of infection, by prophylactic inoculation

In the transmission of bubonic plague, man does not constitute an essential link (*see* figure 102, middle cycle) and, in an outbreak, infected man is an almost negligible factor as a reservoir of infection, for the reasons that the septicæmia seldom reaches the degree necessary for transmission, and that his fleas are poor transmitters Isolation and treatment of the an outbreak pneumonic measure a reasonable precaution

If, however, the rodent–flea–rodent cycle is broken, by attacking the rodent-flea or the rodent, or both, the epizootic will cease and the sporadic infection of man will no longer occur

Prevention must therefore be considered under the following headings —

1 *Isolation and treatment of the sick*
2 *Measures against rats or other rodents*
3 *Measures against fleas*
4 *Protection of man from rats and fleas*
5 *Prophylactic inoculation*

1 *Isolation and treatment of the sick* —There is little more that need be said here under this heading, except it must be remembered that it is mainly against droplet infection in pneumonic plague that protection has to be given to attendants, so that the hospital rooms should be light and airy and wherever possible some form of screen protection should be provided for the personnel

2 *Measures against rats or other rodents* —These measures will constitute insurance against plague infection in any country, but they are naturally more important in an endemic area, and they must be intensified in the presence of an outbreak or when an outbreak is threatened

A plague epizootic amongst the local rat population, or a high infection rate amongst fleas, is the danger signal, and an efficient public health department will, so to speak, keep its finger on the pulse of the rat and flea populations, so that where and when conditions are most favourable for an outbreak the measures may be concentrated

A large number of deaths amongst rats, or of 'rat falls' as they are

Rats will only multiply as long as they are provided with harbourage and food, and the construction of rat proof buildings and particularly rat-proof grain stores is an important measure of prevention of plague. Other general measures include the proper disposal of refuse, the provision of covered receptacles for household garbage, and the rat-proofing of the sewage system.

The domestic cat is a valuable assistant in keeping down the rat population in warehouses, ships, etc.

Rat destruction will of course form an important part of the programme. There are many methods, these include trapping, poisoning, infecting with Danysz virus, and gassing. The last-named is by far the most effective.

There are many forms of **rat trap**; some kill the rats, others capture them alive. It should be remembered that the fleas leave a dead rat, therefore during a plague epizootic it is advisable to use traps which keep the rats alive or which destroy the fleas as well. Rats must then be killed in such a way that their fleas are also killed, or the body should be immediately plunged into strong phenyl or other disinfectant. The dead rat is a grave danger and should be handled only by specially protected personnel.

If the rat-flea population is to be investigated, it will also be necessary to capture the rats alive. They are then chloroformed or placed in a gas chamber, this will kill the fleas also. The fleas are then combed out, counted, and identified.

There are innumerable **rat poisons**. These again should not be used during an epizoötic. Many of them are dangerous to cattle and other animals, and are therefore of limited use. Barium carbonate is however a useful poison because one to two grains will kill a rat, which usually goes into the open—in search of water—to die, whereas dogs can take up to

Gassing has to be carried out by trained squads, but it is by far the

fumigate 100 cubic feet of hold, or warehouse.

For rat burrows, an easier way is to apply the cyanogen gas in the form of a powder from which the gas is given off either slowly or rapidly.

Cymag is such a powder made by Imperial Chemical Industries It contains 20 per cent hydrocyanic acid, and the gas is given off slowly Another form is 'calcid brickettes' which are ground up into a powder and blown into the holes In these cases, all the holes must be effectively blocked up before the gas or powder is pumped in, or the rats escape, this applies particularly to the powders that give off the gas slowly

simp
sium
with 5 drachms of mustard oil are made into a paste, to this a drachm of
per this is rolled into the form
of ped in saturated potassium
chl ie whole candle is dried
thc batti is then thrust into a
rat em-batti gives off sulphur
dioxide which kills rats, but it not so effective against fleas

The measure to be adopted against other rodents will naturally depend on the rodent concerned

In the United States a very elaborate system of investigation of wild … so that, as in the case of rats, the … It is probably this vigilance … the past (*vide supra*) … country movements of rats is … *quarantine regulations are* rightly aimed mainly at the 'deratization' of ships The effect of such regulations is shown in the fact that the U S Public Health Service report that, whereas 50 per cent of ships arriving at Atlantic ports were rat-infested between 1925 and 1927, the percentage had dropped to 8 4 per cent in 1937

The danger is from shore-rats going on board at the infected ports, … Therefore, ships lying along- … the dock, all … discs at least … angles to the hawsers, and … fresh tar and should be raised at night when not in use

3 *Measures against fleas*—*Most of the gassing measures are as* effective against fleas as against rats, and there are few measures that are designed to destroy fleas independently of their rat hosts, as suggested above, care should be taken, when rats are killed, that their fleas perish with them, and both trap and rat should be placed in disinfectant

The floors and particularly the corners of rooms where rats have been found should be pyrethrum sprayed, the strength used for mosquitoes (*q v*), namely, a one-in-twenty dilution in kerosene of the usual concentrated pyrethrum *extract*, will be suitable

Clothes and bedding that are suspected of harbouring fleas can also be sprayed with this

Fleas are likely to be carried from place to place and country to country in grain bags, cotton and jute bails, gunny rolls, etc , and suitable disinfection of any such material coming from an active endemic area should be carried out

4 ***Protection of man from rats and fleas***—The building of rat-proof houses is much easier than the rat-proofing of existing houses The main points in a rat-proof house are that the lower walls and floors should be of hard brick and concrete respectively, and that the former should

sink at least two feet into the ground to prevent rats burrowing under it All ventilators and drains must be protected by iron gratings

During a plague epidemic, evacuation of all infected houses as indicated by 'rat falls' as well as by human cases is an important measure The occupants should not return for several months and then only when the house has been shown to be plague-free by placing caged guinea-pigs in the house for several nights, if they survive the house is probably free from infection

For those working in a plague-infected area and especially those employed on plague duty the clothing should be carefully selected White is preferable, as fleas can be seen easily and picked off Fleas can but do not as a rule bite through clothes The clothes should be such that fleas cannot get inside them, therefore trousers and shorts are unsuitable and should be replaced by knee breeches or 'jodhpurs gum-boots give good protection but the tops should be closed, the sleeves must be tightly bound round the wrists and those handling rats must wear leather or rubber gloves, and an open neck is also a danger, as fleas may fall from the roof

5 *Prophylactic inoculation* —

Historical —Haffkine introduced the inoculation against plague at the end of the last century during the last great pandemic This was the first occasion on which a vaccine had been used on a large scale as a public health measure He used a six weeks-old heat killed (65°C for one hour) culture of *Past pestis* in broth to which 0.5 per cent phenol had been added and gave 4 c cm to an adult Figures collected by the Plague Commission suggested that this inoculation caused an 80 per cent reduction in the infection rate and an 80 per cent reduction in mortality amongst those infected Since this date many millions of doses of this vaccine have been given in India and elsewhere but the statistical value of some of the data that was collected by the Plague Commission and later has been questioned

In 1907, Strong working in the Philippines used a live avirulent strain of plague as a vaccine but this vaccine did not come into general use until 1935 when de Vogel and Otten re-introduced vaccination with an avirulent living culture of plague it has been reported that the immunity produced by this live strain is much higher than that produced by a dead virulent culture This live avirulent strain has now been used in Java for some years and over two million doses given without ill-effects

Although it is not yet finally settled which is the more effective the modified Haffkine vaccine now used in India or the live avirulent vaccine of Otten now used exclusively in Java Madagascar, and elsewhere at present the indications outside India are all in favour of the latter whilst in India the policy at present is to trust a well-tried friend This policy has been influenced by the fact that avirulent live vaccines tend to deteriorate rapidly, so that there would be great difficulties in the way of maintaining stocks and [illegible]

e g [illegible]
mad [illegible]
pher [illegible]
per [illegible]
muc [illegible]

1 0 c [illegible]
very [illegible] they are less though still more severe than with most vaccines The vaccine provides protection for six to eight months

TREATMENT

Good nursing will play a very important part in determining the recovery of the patient He should be confined strictly to bed and not be allowed to do anything for himself, he will want plenty of fluid, possibly drip-feed intravenous glucose, and frequent fomentations to the buboes Further, such possible emergencies as hæmorrhage from septic erosion of large vessels may have to be met

The treatment may be considered under the headings, (*a*) *symptomatic*, (*b*) *local*, and (*c*) *specific*

A **Symptomatic treatment** —The treatment is that for any asthenic febrile disease, for hyperpyrexia, hydrotherapy should be employed, and antipyretic and depressant drugs avoided, the diet should be fluid but nourishing, but since the disease is a short one, it is not necessary to force the calories though the patient should be encouraged to drink freely, imperial drink, barley water, or glucose water Intravenous glucose, 5 per cent, can be given fairly rapidly if there is a lowered blood pressure, but otherwise by the drip-feed method almost continuously

For the generalized pain and restlessness, phenobarbitone should first be tried, and, if this fails, morphia may be given judiciously Digitalis and

oil, or cardiazol

B **Local treatment** —The buboes may play an important part in the

ire vigorous local treatment The fever

uboes develop, and these may cause a

There was an old teaching that it was

missible to put in a scalpel to relieve the pressure and pain When they

pyridine in full therapeutic doses by mouth at this stage is also useful If these sinuses are allowed to become secondarily infected, the course of the disease may be prolonged for weeks or even months

C **Specific treatment** —The present indications are that serum treatment is likely to be replaced entirely by chemotherapy in the near future

Serum treatment —Yersin's serum has no direct action on the

'anti-infectious'

f infection in an

n after excluding

a group of cases for various reasons, a procedure which is always open to suspicion, it has seldom been possible to show more than about a 10 per cent improvement in death rate, *e g* from 74 per cent in 200 controls to 63 5 per cent in serum-treated cases Recently, Sokhey (1936) has produced an anti-serum which has proved more efficacious, and in several series the death rate has been of the order of 25 per cent, with the control series showing about a 50 per cent death rate

The initial dose recommended is usually for 50 to 100 c cm, and this must be repeated daily until the temperature is normal

Chemotherapy.—Prior to the introduction of the sulphonamide drugs, many drugs had been tried without any conspicuous successes, *e g* intravenous iodine, mercurochrome, germanin

Schütze *(1939)* demonstrated *the efficacy of sulphapyridine in plague*-infected rats and mice, and Wagle *et al* (1941) obtained good results in human plague with both sulphapyridine and sulphathiazole, their death [illegible]

doses, and there is an obvious possibility that some of the newer compounds, e g sulphadiazine, may prove more efficacious

PROGNOSIS

This of course will depend on treatment to a large extent

The pneumonic form is always fatal

In published series of treated cases, the control series always have *death rates between 50 and 75 per cent In such series, ambulant cases* and cases of pestis minor will probably not be included, so that the gross death rate is probably less

The prospects of the patient depend on his resistance, and can be measured by the degree of septicæmia from which he suffers In cases with uncontrolled septicæmia and large numbers of bacilli in the blood, the death rate is probably 100 per cent, but, in bubonic cases with only bacillary 'showers', it is *between 25 and 50 per cent*

In the septicæmic case, the patient usually dies within the first five days However, the prognosis should always be guarded, as recovery some- [illegible] a patient who

Death may take place after several weeks from septic complications

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Histopathologically, the local lesion shows a necrotic centre surrounded by an area of polymorphonuclear infiltration, outside which there is some lymphocytic infiltration of the surrounding tissues A similar change occurs in the affected organs, in the lungs, outside the necrotic focus there is a zone of alveolar exudate, and the inflammatory changes may involve a whole lobe and the pleura, and in the liver, the parenchyma cells are invaded and destroyed by *Bact tularense,* and appear as bags of organisms

More chronic lesions which resemble tuberculosis are sometimes observed The necrotic centre is surrounded by an area of epithelioid cells and fibroblasts, outside which is a zone of lymphocytic infiltration, scanty giant cells may be found in these lesions

Blood picture —A moderate leucopenia is the rule, and even in the pneumonic cases the leucocyte count is seldom above 10,000 c mm

SYMPTOMATOLOGY

Clinical types —The usual classification refers to the ulcero-glandular, oculo-glandular, glandular and typhoid types, but this classification is neither satisfactory nor comprehensive In our probably incomplete state of knowledge regarding the scope of *Bact tularense* infection, it will be unwise to adopt any fixed classification, for, as our experience of this disease widens, a satisfactory one will probably evolve

The clinical picture shows considerable variation according to the mode of entry of the causal organisms The most typical symptomatology, and the one that is described below, occurs in those cases in which infection enters through the skin, either through an abrasion or by the agency of an insect, causing a local ulcer and local glandular infection If it enters through the conjunctiva, this structure is first involved and the clinical ... alled oculo-glandular type generally in this type

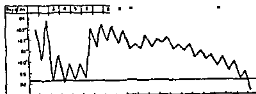
... enlargement or a septicæmia, and produce an attack of the so called typhoid type' This latter is also the form that the disease usually takes when the infection is acquired by eating insufficiently-cooked infected rabbits

Cases have been reported in which meningeal symptoms developed early and the meninges were shown to be infected with *Bact tularense*

Finally, there is the clinical type in which pneumonia is a primary manifestation, as distinct from the pneumonia which may develop as a *complication* in any severe form of tularæmia On analogy with plague and from suggestive epidemiological reports, it seems possible that in some of these cases there is a primary infection of the lung

The clinical course —The incubation period is in the large majority of cases from three to four days, the extremes are 24 hours and ten days The onset is sudden with general symptoms, headache, fever with chilliness, vomiting prostration, and pains all over the body, very suggestive of influenza or a sub-typical dengue The next day, or sometimes earlier, ... the local lesion which now develops into an ulcer, and ... e enlarged and painful The fever rises ... n 24 hours, after two or three days the ... or even to normal for one to three days, and then relapses as a high continued or remittent fever (*see* figure 109), accompanied by fairly profuse sweating, loss of weight and increasing

debility, usually fo
valescence is very

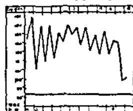

Figure 109 Characteristic chart of uncomplicated tularæmia

out convalescence, or at an early date the glands may become necrotic, suppurate point, and eventually break through the skin leaving a sinus that may not heal for many months Subcutaneous nodules may form along the course of the infected lymph channels, these persist as hard tender movable lumps for some months and occasionally they break down

A rash is sometimes reported but it is not constant, nor characteristic either in its time of appearance or form

The spleen may be slightly enlarged

In the primary pneumonic form the onset is usually with a cough, pleuritic pain, headache, general malaise and a sharp fever usually with chills The temperature continues as a high remittent fever (*see* figure 110) with periodic chills The physical signs are sometimes atypical, and the pleural effusion masks the x-ray picture so that the diagnosis is frequently postponed until the autopsy Milder examples of this type are probably very frequently missed but, judging from the reported cases, one must consider the prognosis very bad


Figure 110 Chart of a fatal case of pulmonary tularæmia (Kennedy

Complications — The commonest are those associated with the local lesions and the glandular infections ulcers and the sinuses that result from suppurating glands may become secondarily infected and persist for months The local eye

(*vide supra*)

DIAGNOSIS

The circumstance may lead one to suspect that a febrile illness is tularæmia, when for example the patient has been bitten by *Chrysops discalis* in an endemic area
been on a shooting expeditı
when he has been in conta
the other hand, many cases have occurred in which the mode of infection was completely obscure

Clinically the combination of a local lesion or conjunctivitis with

The pneumonic type will be particularly hard to diagnose clinically, except that it is a slightly atypical pneumonia with pleurisy, which does not respond to the usual chemotherapeutic agents or to serum

Bacteriological evidence is of course the most desirable, but is not at all easy to obtain On media inoculated with the blood or gland juice growth has been obtained, but not readily, and animal inoculation is the surest method Two to five cubic centimetres of defibrinated blood diluted with an equal amount of normal saline inoculated intraperitoneally into a guinea-pig will produce an infection that will kill the animal within three or four days, with the production of the typical lesions from which *B*- [illegible]

[illegible] test, but this will mostly
b [illegible] 1 in 80 by the third or
fc [illegible] n 5,000 in convalescence

The titre falls slowly, and agglutinins have been reported to persist up to 33 years Sometimes the sera will also agglutinate *Br melitensis* and/or *abortus* (*vide supra*)

An intra dermal test in which 0.05 c cm of a bacterial suspension produces a weal five millimetres in diameter in a positive case, has had a few advocates, it gives a positive result at an earlier date, but it is probably less specific than the agglutination test

PREVENTION

A study of the methods of infection will immediately indicate a number of ways in which the dangers of infection can be obviated, or at least reduced (*vide supra*)

As there is considerable danger of laboratory infection, very special precautions should be taken with regard to the handling and isolation of inoculated animals, *e g* rubber gloves should always be used

Prophylactic inoculation has not proved entirely satisfactory hitherto but recently Foshay *et al* (1942) have shown that some protection is given by inoculation with dead cultures, and that infections in inoculated persons are milder

TREATMENT

No really successful specific has yet been found Serum treatment has been used extensively, and the results of treatment in 600 cases with a similar number of controls have been reported (Foshay, 1938) The results were not very striking, the death rate was 4.2 per cent in the treated cases, but Foshay considered that they demonstrated the value of the serum

Otherwise the treatment is symptomatic Surgical interference with the enlarged glands or the nodules is not to be recommended, open local lesions should be treated with hot saturated magnesium sulphate compresses

PROGNOSIS

During 1938 and 1939, there were about 4,300 cases reported in the United States, with a death roll of about 290, a rate of approximately 6.7 per cent

From the point of view of invalidism, it is a serious disease, as full health is seldom restored under 3 to 4 months, and the average period of hospitalization is often reported as over 100 days In some cases, chronic sinuses have persisted for two years

The cases in which infection was conveyed by eating under cooked rabbits seem to be more serious, and a 60 per cent death rate is reported in one such series

Pulmonary complications cause deterioration in the prognosis, it is reported that 30 to 40 per cent of patients with these complications die, and more than half the patients who die are in this group The death

rate amongst patients with primary lung infections appears to be even higher Those in which meningitis occurs always die

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Recent work—Infectı [illegible] time and recently a stream be [illegible] ntinu-ously over a period of m [illegible] raced and no human infections [illegible]

THE UNDULANT FEVERS

MALTA FEVER

man from animals by various means

Historical —The earliest attempt to separate the first recognized form of this ... n in 1861 he ... l Bruce isolated ... monograph on ... er at this time ... Mediterranean Fever Commission was sent out under the auspices of the British Government to investigate the means of spread of the disease they discovered that goats were the reservoir of infection and that the disease was spread mainly by the agency of goat's milk

Contagious abortion was recognized as a disease of cattle early in the 19th century in Great Britain In 1897 Bang isolated the causal organism of this cattle disease and in 1914 Traum isolated a similar organism from pigs In 1918 Alice Evans demonstrated the close antigenic relation between the causal organism of Malta fever now known as *Brucella melitensis* and the causal organisms of contagious abortion in cattle and in pigs now known as *Brucella abortus* and *Brucella suis* respectively and in 1920 the generic name *Brucella* was adopted

Shortly afterwards Bevan in Rhodesia and Keefer in America recognized certain of the undulant fevers in man in these two countries as abortus fever transmitted from cattle and pigs respectively

Discussion —In our present state of knowledge it seems justifiable to separate this group into the original Malta fever caused by *Br melitensis* and abortus fever caused by *Br abortus* and *Br abortus* var *suis* (or *Br suis*), as there are epidemiological and clinical differences between the two diseases

MALTA FEVER

Definition —Malta fever is a specific disease characterized by fever which may run a prolonged undulant course effusion and pains in the

joints, and an enlarged spleen, it is caused by *Brucella melitensis*, and it is conveyed to man in the milk of goats, amongst which the infection is enzootic, and by other means

EPIDEMIOLOGY

Geographical distribution—Malta fever has a wide distribution and will be encountered in all the zones, except possibly the arctic but the largest numbers of cases occur in the sub-tropics

It is rife in the islands of the Mediterranean and in all the countries of the Mediterranean littoral, and it occurs in many other European countries It occurs in the southern states of America, in Mexico, and in South America, *in South Africa in Iraq, Iran and northern India*, in China, the Dutch East-Indies, and the Philippines, and in northern Australia

Epidemic features—The infection is an enzootic affecting goats and to a less extent other animals, and is transmitted sporadically to man by the ingestion of goat's milk or goat's milk products, and possibly by other

it has shown a tendency to rise again The indigenous population also suffered, but they were usually affected in childhood when the disease is likely to be milder

hostel were infected, apparently

n the

icella

cultures

The incidence varies from year to year and is very definitely seasonal in Malta it occurs in the hot dry months of the year, June to September (*see* figure 111) This seasonal incidence, which is also noted in other endemic areas, *e g* south-east France, where it is a little earlier in the year, is explained on the grounds that it corresponds with the kidding or lambing seasons, but there are other possible explanations (*vide supra*)

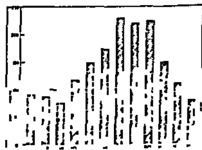


Figure 111 Seasonal distribution of Malta fever (Huddleson 1939)

Persons of all ages are affected and the highest incidence is between the ages of six and thirty Men are said to be most affected, but this may be due to the occupational factor

The disease has an occupational distribution and is common amongst goat-herds and dairy and farm workers

ÆTIOLOGY

The causal organism—When first described by Bruce, the causal organism was named *Micrococcus melitensis*, but later when its relation to the other organisms causing undulant fever was recognized (*vide supra*), the genus *Brucella* was created and this organism was renamed *Brucella melitensis*

Br melitensis is a cocco-bacillus 0 3μ to 0.5 μ in diameter, with oval or even bacillary forms which may be as much as 2 0μ in length It is non motile non-sporing and occurs singly, in pairs or even in short chains It is gram-negative

Culture —It grows on ordinary nutrient agar but very slowly, it will grow [illegible]

months It will survive for many months in laboratory medium Laboratory infections are relatively common

Pathogenicity for laboratory animals —*Br melitensis* readily causes infection in monkeys, but not always in guinea-pigs, whereas *Br suis* is very virulent in the latter, *Br abortus* is very variable in its pathogenicity, but falls between the other two species in its pathogenicity in guinea-pigs

Distribution in the body secreta and excreta —The organisms are present in the blood during the fever They occur in large numbers in the spleen, from where they can be recovered during life by spleen puncture, or after death They occur in the urine in about 10 per cent of cases, and the urinary infection may persist for some months They have been isolated from human milk They can also be demonstrated in the fæces by a special technique

Portals of entry —The usual means of infection is by the gastro-intestinal tract but the organisms can also enter with comparative ease through the conjunctival, nasal, or naso-pharyngeal mucous membranes, and also through the skin, but in the latter case entry is probably effected through small abrasions Laboratory infections are very common, and recently in the United States 57 laboratory infections were reported from 17 laboratories The persistence of the infection in the British army and navy in Malta even after all consumption of goat's milk had been stopped, the higher incidence in the dry dusty season the ability of the causal organisms to resist drying, and the fact that goats pass them in their urine, all suggest the possibility that entry through the nasal and respiratory mucous membranes may play an important, though secondary, part in the epidemiology of the disease

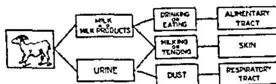


Figure 112 Schema showing the origin media and mode of transmission and route of entry of the infecting organisms in Malta fever

Differentiation of *Brucella* species —There are two antigenic elements present in different proportions in the three allied organisms, the antigenic structures are shown diagrammatically in figure 113

Thus, the organisms cannot be separated by straight agglutination, but *Br melitensis* can be separated from the *abortus-suis* group by absorption of agglutinins The brucellæ can also be differentiated by means of their growth in the presence of certain dyes, the following table, which is taken

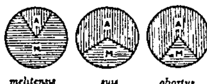


Figure 113 Diagram indicating the proportions of the antigenic elements M and A in the three recognized species of *Brucella*

with minor modifications from Topley and Wilson (1936), summarizes the means of differentiation —

Type	Usual habitat	Grown in absence of extra CO_2	Growth in presence of: Basic fuchsin 1 in 25 000	Thionin 1 in 50 000	Methyl violet 1 in 100 000	Pyronin 1 in 200 000	H_2S formation	Antigenically
melitensis	Goats sheep	+	+	+	+	+	−	*melitensis*
abortus	Cows horses dogs	−	+	−	+	+	+	*abortus*
American *suis*	Pigs	+	−	+	−	−	+	*abortus*
Danish *suis*	Pigs	+	−	+	−	−	−	*abortus*

Immunity —One attack does not appear to confer complete immunity against a subsequent attack but the second attack will be mild

The fact that the organisms circulate in the blood for a number of days does not suggest the early formation of immune bodies, agglutinins usually appear, but they may be of low titre and are not constantly present

No satisfactory immunity can be produced by inoculation of dead cultures

PATHOLOGY

Moi
has beer
are few
deaths a
clouds the true picture

The spleen is nearly always enlarged it is soft and hyperæmic Occasionally there are small hæmorrhages and infarcts

Histologically the sinuses are dilated there is proliferation of the reticulo endothelial cells, and a hyperplasia of the lymphoid tissue

There is often slight enlargement of all the lymphatic glands but especially those of the mesentery In the intestines there is sometimes slight congestion of a few Peyer s patches but there is neither ulceration nor even any other constant changes in the intestinal lymphoid tissue

The sygmoidoscope sometimes shows a granular colitis This causes a watery diarrhœa that appears to respond to specific vaccine therapy

Blood picture—There is usually anæmia and this tends to be progressive red cell counts are sometimes below 3 000 000 but seldom if ever below 2 000 000 per c mm in an uncomplicated case There is a slight tendency towards a leucopenia but this is neither marked nor constant, however the count in an uncomplicated case is never above 10 000 per c mm and sometimes as low as 4 000 per c mm The differential count is more characteristic the lymphocyte count often amounts to 50 per cent of the [illegible] tes and there is a fairly constant large mononuclear increase

an actual granulopenia

ial features beyond the usual febrile

and may contain a trace of albumin

As noted above brucellæ can be isolated from the urine in about 10 per cent of samples

SYMPTOMATOLOGY

The incubation period is from 10 to 15 days the extremes being from 5 to 17 days as a general rule but in exceptional cases it may extend to 40 days

There are mild prodromal symptoms malaise and headache followed by a slow onset of fever increasing lassitude and inability to concentrate pains all over the body and particularly in the joints pains in the eyes on lateral movement anorexia insomnia and irritability The fever in [illegible]

non inflammatory hydrarthrosis of the painful joints Mild abdominal symptoms may develop congestion and discomfort usually with constipation but occasionally with watery diarrhœa the tongue is very furred The pulse is soft rapid and irregular Bronchial symptoms are common The spleen may in time become enlarged it is usually soft and tender There is increasing toxæmia in severe cases but in the average case the patient does not feel particularly ill finds bed irksome and is very irritable

The fever reaches its highest point in about a week it remains as a high remittent or continuous temperature for possibly another week and then step ladders down reaching normal usually within three weeks it

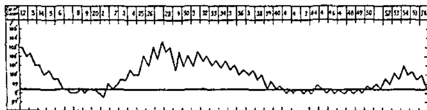


Figure 114 Temperature chart of a case of Malta fever (orig)

joint pains are the rule

Other symptoms are orchitis or mastitis neuritis *e g* facial and intercostal neuralgia sciatica and lumbago and more rarely temporary paralyses Sometimes there is blurring of the vision and vertigo In the long continued cases loss of weight and even emaciation will be an important symptom

In severe cases there may be purpuric spots oozing from the mucous *membranes and even profuse bleeding into the stomach intestine or* bladder

[illegible] to pulmonary tuberculosis The usual lung complication is bronchitis but bronchopneumonia is not uncommon Other complications are parotitis suppurative orchitis and arthritis pregnant women usually abort.

with minor modifications from Topley and Wilson (1936), summarizes the means of differentiation —

Type	Usual habitat	Grown in absence of extra CO_2	Growth in presence of Basic fuchsin 1 in 25 000	Thionin 1 in 50 000	Methyl violet 1 in 100 000	Pyronin 1 in 200,000	H_2S formation	Antigenically
melitensis	Goats sheep	+	+	+	+	+	−	*melitensis*
abortus	Cows horses dogs	−	+	−	+	+	+	*abortus*
American *suis*	Pigs	+	−	+	−	−	+	*abortus*
Danish *suis*	Pigs	+	−	+	−	−	−	*abortus*

Immunity —One attack does not appear to confer complete immunity against a subsequent attack, but the second attack will be mild

The fact that the organisms circulate in the blood for a number of days does not suggest the early formation of immune bodies, agglutinins usually appear, but they may be of low titre and are not constantly present

No satisfactory immunity can be produced by inoculation of dead cultures

PATHOLOGY

hanges has there are t such deat which clouds the true picture

The spleen is nearly always enlarged, it is soft and hyperæmic Occasionally, there are small hæmorrhages and infarcts

Histologically, the sinuses are dilated, there is proliferation of the reticulo-endothelial cells, and a hyperplasia of the lymphoid tissue

There is often slight enlargement of all the lymphatic glands but especially those of the mesentery In the intestines, there is sometimes ... of a few Peyer's patches, but there is neither ulceration, the intestinal lymphoid tissue ws a granular colitis This causes a watery diarrhœa that appears to

Blood picture.—There is usu pro- gressive red cell counts are someti ever below 2,000,000 per c mm in an light tendency towards a leucopenia, but this is neither marked nor constant, however, the count in an uncomplicated case is never above 10 000 per c mm and sometimes as low as 4,000 per c mm The differential count is more characteristic, the lymphocyte count often amounts to 50 per cent of the total leucocytes, and there is a fairly constant large mononuclear increase,

ile un

As noted above, brucellæ can be isolated from the urine in about 10 per cent of samples

SYMPTOMATOLOGY

The incubation period is from 10 to 15 days, the extremes being from 5 to 17 days, as a general rule, but in exceptional cases it may extend to 40 days

There are mild prodromal symptoms, malaise and headache, followed by a slow onset of fever, increasing lassitude and inability to concentrate, pains all over the body and particularly in the joints, pains in the eyes on lateral movement, anorexia, insomnia, and irritability The fever increases step ladder wise, as in typhoid, and reaches 102° or 103°F in five

[illegible]

non inflammatory hydrarthrosis of the painful joints Mild abdominal symptoms may develop congestion and discomfort usually with constipation, but occasionally with watery diarrhœa, the tongue is very furred The pulse is soft, rapid, and irregular Bronchial symptoms are common The spleen may in time become enlarged, it is usually soft and tender There is increasing toxæmia in severe cases but in the average case the patient does not feel particularly ill, finds bed irksome and is very irritable

The fever reaches its highest point in about a week it remains as a high remittent or continuous temperature for possibly another week and then step ladders down, reaching normal usually within three weeks, it

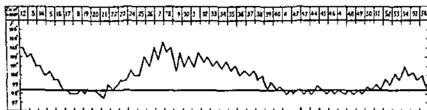


Figure 114 Temperature chart of a case of Malta fever (orig)

may remain normal for a day or two and then it starts to rise again The waves are not usually regular but on the average they maintain about a three week periodicity With the relapse of the fever, the symptoms tend to return but not usually in such a severe form though sweating and fleeting joint pains are the rule

Other **symptoms** are orchitis or mastitis, neuritis, *e g* facial and intercostal neuralgia sciatica, and lumbago and more rarely temporary paralyses Sometimes there is blurring of the vision and vertigo In the long continued cases, loss of weight and even emaciation will be an important symptom

In severe cases there may be purpuric spots, oozing from the mucous membranes, and even profuse bleeding into the stomach, intestine, or bladder

[illegible]

[illegible] fever does not predispose the patient to pulmonary tuberculosis The usual lung complication is bronchitis but bronchopneumonia is not uncommon Other complications are parotitis, suppurative orchitis, and arthritis, pregnant women usually abort

Clinical types —As in most other diseases, *the individual's response* to the infection will vary The following clinical types can be recognized :—

re of any illness,
nalaise In any
ation will bring
high agglutina-

(ii) *The mild* —In this type there is only a single bout of fever lasting perhaps a fortnight, or a mild bout and one short relapse

(iii) *The classical* —The attack of moderate severity, as described above, with repeated relapses lasting several months

(iv) *The chronic* —The disease may start as an ordinary or mild
of any acute febrile attack, and
there is little sign of the usual
joint pains and sweating occur
ent —In this type the patient
than in the
nths without
of the un-

ed toxæmia,
-like course,

DIAGNOSIS

Discussion — It is justifiable to make a provisional diagnosis on clinical grounds, and in certain circumstances it may be permissible to maintain it without confirmation from the laboratory, but, obviously, confirmation should be obtained whenever possible

With proper laboratory facilities, it should be possible to isolate the causal organism in half to three-quarters of the cases seen early in the
those first coming under observation
relied upon Of these, the agglutina-
-dermal test should certainly be done
glutination test is negative, and the
opsono-cytophagic test may be used as the third or as a confirmatory method

A *Clinical.*—The principal points are —high fever with little pros-

bic
er
ap
ay
ve

for at least 12 days

The urinary culture is said to be positive at some stage of the disease in 75 per cent of cases, but the general experience is that 10 per cent of specimens of urine will give a positive culture, the statements are not incompatible

C ***Specific antibody tests*** —(*i*) **Agglutination** —This is considered the most reliable of the specific tests, other than the isolation of the causal

organism, in most cases the agglutinins appear in the blood between the fifth and tenth days, and remain for a long but variable time for many years in some cases and for one year in the majority Agglutinins are not, however, constantly present even in the acute stages of the disease, and ... th

... or

... re

should be expected

The agglutination test is not species specific, and there is usually no significant difference between the titres obtained with *Br melitensis* and *Br abortus* emulsions, but, after the minor agglutinin (*see* figure 113) has been absorbed, agglutination will occur with the specific antigen with

... in this test is to prepare or ... 'Brucellergin', as prepared by Huddleson (1934), is probably the best, but if neither this nor any other standardized preparation is obtainable, one can be made from a heat-killed fat-free bacillary emulsion Reactions are apt to be sharp and there may even be constitutional symptoms, so that a 1-in-100 dilution of the standardized 'brucellergin' should be used first, and later, if a negative result is obtained, a 1-in-10 dilution

...

occurs

...

Outline of technique and interpretation of results —To 5 c cm of blood, 0.2 c cm of 20 per cent sodium citrate is added a bacillary emulsion of 6 000 million organisms (or equivalent to a suspension of 300 parts per million of silica) in normal saline is made one cubic centimetre of each of these two is mixed in a test tube which is put into an incubator at 37°C for one hour, the sedimented d ... on clean slides these are dried rapidly, t ... smear is fixed and stained The slide i ... the number of polymorphonuclears that h

...

Differential diagnosis —The disease may simulate any of the long-continued fevers of temperate or tropical climates

The cosmopolitan diseases include—tuberculosis, especially of the lungs and intestinal tracts, the enteric fevers, rheumatic fever and rheumatism, *Bacillus coli* infections, and the Pel-Ebstein syndrome in Hodgkin's disease

Amongst tropical diseases, kala-azar is the most likely to lead to confusion, there are *many points of similarity* the long continued undul-
azar the bouts of fever are usually o
—but this is usually more pronounced
ration and the slow establishment of debility, and the granulopenia—which again is more marked in kala-azar Untreated malignant tertian or relapsing benign tertian malaria, and also amœbic hepatitis with abscess formation may simulate Malta fever, but in both these diseases the therapeutic test should clear up matters, and in liver abscess there is *usually* a leucocytosis

PREVENTION

The following are the three main lines along which *attempts at prevention* should be made —

(i) The elimination of the source of infection primarily in goats sheep and cattle

(ii) The prohibition of the use as food or the sterilization of the medium of infection

(iii) The protection of susceptible and exposed persons e g by education and *if necessary regulations and by inoculation*

(i) *The elimination of the source of infection* —The destruction of the

has not proved very successful, but this is a matter for further veterinary research

It is probably very seldom that an infected person is a serious source
bacteria may be passed in the
excreta is a preventive measure

ood, or the sterilization, of the medium of infection —The prohibition of the consumption of milk or milk products, or the enforcement of pasteurization will be successful only if the consumption of infected milk is the sole or main means by which infection is acquired Even in Malta there is some doubt on this point, though prohibition of the use of goat's milk and goat's milk products by army and navy personnel appeared to be completely successful for some years In other places, e g the south of France, where the disease occurs mainly amongst dairy workers, there are obviously other channels of infection

Pasteurization will kill the brucellæ, and if this procedure can be enforced, *this means of spread of the disease will be effectively controlled*

(iii) *Protection of susceptible and exposed persons* —Dairy and other workers should be warned to wash their hands before taking food, and to keep their hands *free from abrasions*
n with killed cultures of brucellæ
very disappointing More work
fore this measure can be recom-
mended as a routine

TREATMENT

DISCUSSION —The state of the treatment of Malta fever is at present far from satisfactory The introduction of the sulphonamide preparations raised hopes that a specific might *be found for this infection*, and many enthusiastic reports appeared in the medical press, these early reports were soon followed by cautionary, and eventually by frankly condemnatory

ones As a new chemotherapeutic drug appears almost monthly it is impossible to keep up to date and it would be foolish to be dogmatic on this subject and to dismiss them all, further one hopes that some day a specific of this nature will be found Meanwhile it will be necessary to

successful methods

Even here it is not possible to

ide range of clinical states In

ept in bed and careful nursing

eating will necessitate frequent

pains will require local applications and in the later stages massage to the wasted limbs will be helpful

After a severe febrile bout the patient should be kept in bed for four or five days after the temperature has fallen to normal especially in a cold or temperate climate where chills are likely later when the disease enters on its more chronic stages it will usually not be possible to maintain this routine and it is questionable if it is necessary to limit activities except during the febrile attacks (Some writers recommend long continued con

finement to bed to o

in the clinical course

cases would have to l

be proved It does

advocated it)

The diet should be as liberal as possible but naturally during the

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c

In acute toxæmic cases a pint of 5 per cent glucose may be given intravenously every day this will combat dehydration assist detoxication and provide nourishment

Vaccine therapy — On the whole vaccine therapy seems to have pro duced the best results especially in chronic cases The aim should be to

should determine the next

Vaccines should not be given during the high febrile stages nor when toxæmia is marked and in these stages serum therapy is indicated

Serum therapy.—This should be used only in the acute and toxæmic stag of 50 to 1 saline or 5

beer s have cases when joint pains are troublesome, good results have been claimed, particularly in relieving some of the tiresome symptoms

Chemotherapy.—Dyes have been used for some time with varying results Some success has been claimed for acriflavine, a maximum dose of 10 milligrammes per kilogramme body-weight, *i e* 0 7 gramme for the average adult, was given intravenously

Trypaflavin has also been used, 10 c cm of a 2 per cent solution is given intravenously, once a week A special precaution is that patients must be kept in a darkened room, as during this treatment they become very sensitive to light Good results have been claimed with these dyes, but their administration is not entirely without risk

Many of the new 'sulpha-' preparations have been tried, but so far, as stated above, without any uniform success The writer has used sulphapyridine and sulphathiazole, without very convincing results The chart of one case recently treated is shown (figure 115), it seems possible that the sulphathiazole controlled the fever, but our experience here is that a spontaneous cure often occurs after one or two bouts Recent reports on sulphapyridine suggest that the history of the early reports on sulphonamide (*vide supra*) is being repeated The writer has seen no reports on treatment with sulphadiazine

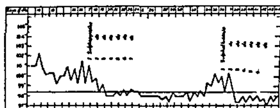


Figure 115 Temperature chart in Malta fever Sulphapyridine appeared to control the fever, but a relapse occurred which again appeared to respond to sulphathiazole

Neither sulphanilyl-guanidine nor succinyl sulphathiazole, which are so useful *in the dysenteries, is likely to be useful in this disease on account* of their low absorption

PROGNOSIS

The average duration of the illness in frank clinical cases is at least two months, but durations up to two years have been reported

The death rate amongst such cases is from 2 to 5 per cent

three

ABORTUS FEVER

Discussion—As abortus fever is so closely related to Malta fever, only the points of distinction will be dealt with here

(or *Br abortus* var *suis*) are the cultural differences and in the table on page 356

Br abortus and *Br suis* cause enzootic infections in cattle and pigs,

stribu-
Great
is very
rare,
operly
investigated that can claim freedom from this infection

Epidemic features —Infection is transmitted from cattle and pigs to man in a number of ways, which are best shown diagrammatically, *see* figure 116 below

Abortus fever has an even more definite occupational distribution than Malta fever and is very prevalent amongst meat packers who handle pig carcases amongst stockyard workers butchers, and veterinarians as well as amongst farm and dairy workers

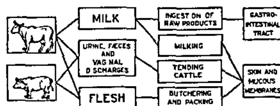


Figure 116

SYMPTOMATOLOGY

On the whole, the disease tends to run a much more benign course than Malta fever, this applies particularly to *Br abortus* infections The vast mbulant, (ii) mild and (iv) types are rare but are enot negligible

commonest symptoms are malaise headache sweating, a marked tendency to lassitude and fatigue, vague body pains, rigors, constipation and anorexia, more or less in that order of frequency, from 100 per cent down to about 60 per cent, in frank cases The spleen is sometimes enlarged but less frequently than in Malta

Br suis infections are on the whole much more severe than *Br abortus* infections, *Br abortus* infections acquired in the laboratory seem to be much more severe than those acquired naturally All *Br suis* infections and laboratory infections with *Br abortus* are nearly always acquired through the skin or mucous membranes whereas natural *Br abortus* infections are acquired *via* the gastro intestinal tract It seems possible therefore that the route of invasion has some effect on the severity of the infection

The **prognosis** *is distinctly better in Br abortus infections than in* Malta fever and *Br suis* comes between the two

DIAGNOSIS

Und

above

to obtain

to this infection can be taken advantage of, and guinea pig inoculation should be added to the bacteriological methods

citrated blood should he sediment from the nk or groin *ed on the guinea pigs* and from the organs

particularly the spleen smears and cultures are made

Br abortus infection in milk can usually be detected only by animal inoculation 2 to 5 c cm of separated cream is injected into each groin

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MELIOIDOSIS

Definition.—*Melioidosis is a fatal disease of protean symptomatology*, caused by a glanders like bacillus *Pfeifferella whitmori* (*pseudo mallei*) which is transmitted to man sporadically from rats amongst which it is epizootic in certain eastern tropical countries

Discussion.—The excuse for the inclusion in this book of a disease of which only about a hundred cases have been reported in the 30 years since it was first described, is that there are reasons to believe that it is much more widespread than our present knowledge appears to indicate

Historical.—Whitmore and Krishnaswami (1912) described a disease that they

ÆTIOLOGY

In most laboratory animals, they produce a fatal septicæmia as well as a local abscess when injected In the guinea-pig a small dose given intraperitoneally will cause a painful swelling of the testicles in two days (Straus's reaction), a large dose will kill the animal before this reaction has had time to occur

Infection of animals will also occur after oral administration The organisms are excreted in the fæces and urine of infected animals

In man, it produces a septicæmia and/or a pyæmia, and can be recovered from most tissues of the body after death

Transmission takes place mainly by the oral route, it is believed, by contamination of food by rat's fæces and/or urine

EPIDEMIOLOGY

agrants or persons of the
sociation with rats

PATHOLOGY

The essential pathological lesion is a nodular focus similar to miliary
an abscess
em, how-
inal fluid
confined
o amœbic

SYMPTOMATOLOGY

Very few cases have been diagnosed ante mortem, and in these the symptomatology has shown wide variations The earliest reported cases had cholera-like symptoms—a watery diarrhœa, vomiting and collapse with death within two or three days, other cases have shown pneumonia-like symptoms and death has been postponed by several days, and in yet others a pyæmic condition has been reported, with subcutaneous abscesses or even a cutaneous eruption simulating smallpox In this last group, the patients usually survive for two or three weeks, in some cases death has occurred after two months, and two patients have eventually recovered

ith such a varied
al diagnosis presents
laboratory medium
ic abscesses Where
material should be
inea-pig, this latter
l taken from decom-

a dilution of 1 in 3,000 was reported in the blood of one surviving patient This method may prove of use *for making* a diagnosis in less acute cases

Prevention and treatment —In our present state of knowledge, no preventive measures other than the destruction of rats and the protection of food from contamination by these rodents can be advocated

Treatment is entirely symptomatic Obviously, the new chemotherapeutic agents should be given a trial

Prognosis —Only two patients have been known to survive

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THE INTESTINAL FLUXES

Introduction —The treatment of fever and the intestinal fluxes forms at least 90 per cent of the daily routine of the practitioner in the tropics, in malarious districts, fever will probably claim the greater share of his attention, but even here the fluxes will come a close second, in other districts they will be an easy first The causes of diarrhœa are numerous
away from the intestinal
early every organ in the
an unimportant symptom
ncer, syphilis, and tuber-
ell defined ætiology, such
lisease), and mechanical
he bowel which will pro-
ification will therefore be
more important forms of
intestinal flux that have some special association with the tropics, most of these have a specific and recognized ætiology

CLASSIFICATION AND DEFINITIONS

A **Cholera** —An acute specific diarrhœa caused by *Vibrio choleræ*, in which the small intestine is mainly involved

B **Dysentery** —*A clinical condition in which frequent stools containing* blood and mucus are passed, with tormina and tenesmus Ætiologically, dysentery can be placed under a number of headings —

I Caused by bacteria

(i) Shiga dysentery —A very severe dysenteric condition, always acute in its early stages, caused by *Bacterium dysenteriæ* Shiga

(ii) Flexner group dysentery —A dysenteric condition, sometimes *severe, and usually acute in its early stages, caused by a group of organisms* of the type *Bacterium dysenteriæ* Flexner

(iii) Sonne type dysentery —A dysenteric condition, usually of a milder
caused

(iv
followed by dysenteric symptoms, associated with infections of the Salmonella group, *Salmonella paratyphosus B enteritidis*, and *typhimurium*

II Caused by animal parasites

(a) Protozoal dysentery (i) Amœbic dysentery —Primarily a dysenteric condition usually with an insidious but *occasionally an acute onset,*

(iii) Ciliate dysentery ... e but serious dysenteric condition caused by *Balantidium coli*, a ciliate common in pigs

(iv) Coccidiosis.—A rare diarrhœal or dysenteric condition caused by *Isospora hominis*.

(v) Malarial dysentery.—A dysenteric condition associated with an intense *Plasmodium falciparum* infection.

Leishmanial dysentery is often included under this heading, but the evidence is against there being any such specific condition. In experimental animals, and to a less extent in man, the mucous membrane of the intestine is often heavily infiltrated by leishmaniæ, but histologically there is no tendency towards ulceration. The ulceration that occurs as a complication, often a terminal one, is due to some other infection, and/or to malnutrition.

(b) **Metazoal dysentery.** (i) **Bilharzial dysentery.**—A dysenteric condition caused by the eggs of helminths of the genus *Schistosoma* (*Bilharzia*).

(ii) **Other helminthic dysenteries.**—Diarrhœal and dysenteric conditions caused by helminths of the genera *Œsophagostomum*, *Heterophyes*, *Fasciolopsis*, and *Strongyloides*.

(c) **Viral dysentery.**—In *lymphopathia venereum*, proctitis which may develop into a severe ulcerative condition of the rectum or sigmoid often occurs. This ulcerative condition is usually above a stricture, but it may follow or precede stricture formation.

C. *Chronic ulcerative colitis.*—A chronic non-specific ulcerative condition of the colon that is very frequently the sequel to one or other of the acute specific dysenteric conditions classified above; this is a condition that is well known in temperate countries but is far more common in the tropics.

D. *Diarrhœal diseases that are probably dietetic in origin.*

(i) **Sprue.**—A disease of disordered metabolism in which the passage of frequent frothy and fatty stools is a very prominent symptom, usually occurring in Europeans living in a tropical country, under abnormal dietetic conditions.

(ii) **Para-sprue.**—A diarrhœal disease due to multiple, often self-imposed, dietary deficiencies associated with anæmia and disordered carbohydrate metabolism, and common amongst residents—indigenous and otherwise—of tropical countries, but not peculiar to them.

(iii) **Other nutritional diarrhœas.**—Diarrhœas that are important but not the main symptom of other nutritional diseases, e.g. pellagra (q.v.).

E. *Diarrhœas of special environmental conditions.*

(i) **Hill diarrhœa.**—A disease of mixed ætiology but possibly associated with the atmospheric conditions at high altitudes.

(ii) **'Gippy tummy' and allied conditions.**—A diarrhœal condition, probably mainly of bacterial origin, precipitated by local chilling, occurring in dry tropical and sub-tropical countries (e.g. Egypt) where there is a high diurnal range of temperature. (No further reference will be made to this condition, about which there has been much correspondence in the medical press recently; the general opinion is that it is usually caused by one of the recognized dysentery organisms and precipitated by sudden chilling.)

CHOLERA

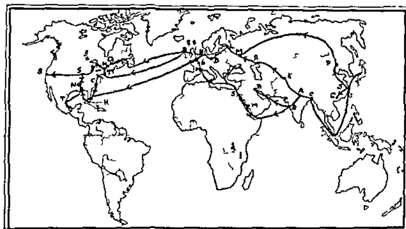
Definition —Cholera is an acute specific often fatal disease characterized by very copious watery and colourless stools vomiting and symptoms attributable to fluid loss and toxic absorption notably collapse, muscular cramps and suppression of urine it is caused by the cholera vibrio, and occurs endemically in certain localities in India and China and may spread as an epidemic throughout the world

Historical.—The antiquity of cholera is doubted by many historians and certainly there is little evidence that any of the early historical plagues that fell upon countries and wiped out armies were cholera In ancient Indian medical writings Susruta described a condition that might well have been cholera but the χολερα of Hippocratic writings was not this disease as the word literally means a flow of bile

One of the earliest historical references to the disease is a reference to the
...e by cholera in 1438 Bontius described
in 1629 Chinese writers have claimed
in about 1669 but there is a school of
and the early Chinese writers were
describing dysentery

The first and worst historical pandemic started in India in 1817 and spread in a number of directions —(a) by land to China (1818) (b) to Ceylon (1819)
e Philippines China
nd thence to Russia
Europe A second
course but on this
two directions t a
reached Moscow in

September 1830 from there it spread to Leningrad (June 1831) Berl n (August) Hamburg (October) and thence across the North Sea to Sunderland in Great Britain and it reached Ed nburgh in June 1832 Later it crossed to America



F gure 116a Routes taken by cholera two pandem cs start ng from Cal utta (C) in 1827 and 1842

A	Astrakan	1830	July 20	1847	June
M	Moscow		Sept		Sept
L	Leningrad	1831	June 16	1848	June
B	Berl n		Aug 31		
H	Hamburg		October		Sept
S	Sunderland		Oct 24		Oct 4
E	Edinburgh	1832	Jan 22		October
Q	Quebec		Apr l		
N Y	New York		June		Nov 9
N O	New Orleans	1833	Jan		Dec 8

1865 pandem c start ng from Hindu Kumbh mela reached Bombay then e to Mecca by Mohammedan p lgr ms

B	Bombay	1865	Apr l
M	Mecca		May
S	Suez		May
M	Marse lles		July
P	Par s		July
E	England		August
N Y	New York	1866	May

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Health
s disease
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ve been

enforced and wh ch control the spread not only of cholera but of many other

even in a scientific world ripe for the acceptance of any new bacteriological discovery. Some of the bacteriologists of the day seemed to think that Koch had displayed rather bad taste in introducing a curved organism where they had expected a straight one. His theory however soon received general credence and the matter was left where it stood for some years. The application of the agglutination test and Pfeiffer's phenomenon at first seemed likely to clarify the [illegible]

In this confused atmosphere the Health Organization of the League of Nations constituted a cholera commission and the Indian Research Fund Association decided to devote a considerable sum to cholera investigations. Bacteriological investigations in the Standards Laboratory at Oxford (Gardener and Venkatraman 1935) and the National Institute of Medical Research at Hampstead with the collaboration of field workers in India have led to a considerable clarification of the position as it stands to-day (*vide infra*).

ÆTIOLOGY

[illegible]

have a common H antigen but a number of O antigens that divide this group into many sub groups; the important one is O sub group I which includes the true non hæmolytic cholera vibrio and the hæmolytic El Tor vibrio. Of the true cholera vibrios there are two sub types 'Inaba' and 'Ogawa'.

Thus the true cholera vibrio is a non hæmolytic vibrio that is agglu- [illegible]

cholera.

The cholera vibrio. Morphology and cultural characteristics.—*Vibrio choleræ* is a motile comma shaped organism 1.5 to 4 μ long by 0.2 to 0.4 μ in thickness with a single polar flagellum staining easily with weak carbol fuchsin, gram negative and growing easily on ordinary bacteriological media at 37°C. (*see* plate B)

On agar plates the colonies are round 1 to 2 mm in diameter low convex translucent greyish yellow with a smooth or finely granular glistening surface and entire edge of amorphous or finely granular structure of the consistency of butter and easily emulsifiable. On horse-blood agar plates after 24 hours at 37°C there is an abundant growth and the colonies are surrounded by a 2 mm zone of hæmolysis; there is however no true

The cholera ...

... true non-haemolytic cholera vibrios

By carrying out these three tests, strong, though still presumptive, evidence is obtained regarding the ...
to say, with very few ...
type I, and will give ...
reaction, and if it do ...
a true cholera vibrio

Resistance.—The cholera vibrio has no resistant phase, it survives on clothes from one to three days in a moderately moist atmosphere, but is easily killed by drying It dies in sewage within 24 hours In pure water it dies rapidly, but in some 'potable' waters it will survive for a considerable time

For the survival and multiplication of the cholera vibrio, salt and organic matter are necessary in the water, the higher the concentration of the former the lower need the latter be, and *vice versa* The limits for multiplication are 1 per cent salt (sea salt) with 1 in 500,000 peptone, and 0 1 per cent salt with 1 in 500 peptone, for survival the range is distinctly wider, for example vibrios will survive for some weeks in 0 02 per cent salt and 1 in 5,000,000 peptone The hydrogen-ion concentration limits are pH 6 0 and pH 9 4 ...

Many natural ...
lent to 1 in 5,000 to ...
per cent

It is killed at 55°C in 15 minutes, in 0 5 per cent phenol in a few minutes, and in 1 in 500,000 ...

Bacteriopha...
lyse the cholera ...
Two of these, A ...
cholera vibrio only ...
... in any
anim... roduced
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ceptible to the toxic action of the vibrios and to the products of their ... given by ... ly lost ... they are ... ich of its
pathogenicity in culture

Personal susceptibility also plays an important part, Macnamara reported an incident in which 19 persons ate a meal heavily contaminated by a cholera stool and only 5 developed classical cholera An incident

* *Cholera-red reaction* Ten cubic centimetres of peptone broth (peptone—1 per cent, sodium chloride—0.5 per cent in distilled water, adjusted to pH 8 0) is ... 37°C
inoculate ... a pink
Four to ... colour
colour in ... ndered
usually c...
negative

† ... icose-phosphate ... of this culture ... cm of 40 per ... a pink colour ... rs ... brand and this ... precaution also

happened in the writer's personal experience when cholera infection was introduced into the children's ward of a hospital, in so-called skimmed milk —probably milk diluted with dirty water—that he had ordered for a child with infantile cirrhosis of the liver There were six children in the ward, two died of cholera, two had a mild diarrhœa, and two had no symptoms at all From the stools of all six patients, cholera vibrios were isolated

Toxins.—This is always a controversial point The general opinion is that there is no true soluble exotoxin secreted, but that there is an

duce an exotoxin *in vitro*, it may do so *in vivo*

Distribution in the body.—The vibrios are confined almost entirely

n, and they are usually

They do not penetrate

nd biliary passages are

olated from pneumonic

patches in the lungs

Mode of escape from the body.—Vibrios escape from the body in the stools and in the vomitus, but recent investigations have shown that they cannot be isolated from the urine if measures are taken to avoid fæcal contamination of the urine (Chatterjee and Malik, 1938) The patient does not usually pass true cholera vibrios in the stools for more than five days from the time of first infection, this is also true in the sub-clinical (or contact) case of cholera infection In a few instances, 'carriers' have been detected who passed cholera vibrios up to two weeks but it is very doubtful if there is a true carrier state in cholera as there is in typhoid (Taylor, 1941); in this connection, reports previous to 1935 must be discounted, on account of the doubt that exists regarding the true identity of the organisms passed The human source of cholera infection is thus cases and contacts (sub-clinical cases)

acidity

Media of infection.—The commonest medium of infection is water Other fluids also, particularly milk, will carry the infection Uncooked foods and any food allowed to remain uncovered are common media of infection, especially during an epidemic, *e g* fruit and vegetables which may have been sprinkled with water taken from any wayside source, to keep them fresh, food exposed for sale in the open bazar and by itinerant sweet-meat vendors,

and left expos

Active ag

probably the

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morbid material

Immunity.—There is evidence that, in man, some—though possibly not complete—natural immunity exists It has been claimed that new-

comers to an endemic area are more susceptible than the indigenous inhabitants, but in this disease there is much less evidence of acquired herd immunity in the endemic areas than there is in the case of many other endemic diseases, for periodic exacerbations frequently occur with very high incidence and death rates

One attack does not give protection against a subsequent attack. Though a second attack within a few years is uncommon, the author knows of two instances in which patients had three attacks of cholera within 16 and 10 years respectively, in the former case, two of the attacks were bacteriologically proven, and in the latter one attack was bacteriologically proven, but all three were typical severe attacks and the second was the most severe

Active immunity can be induced by inoculation, but it is very short lived and lasts only for six months at the outside

Active immunity can be induced in animals by the injection of killed

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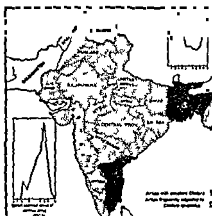
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EPIDEMIOLOGY

Endemic centres —The most important epidemic centre of cholera in the world is undoubtedly in Bengal, the origin of most epidemics in India some of which have become pandemics, can be traced to Bengal, but there is evidence that there are, now at least, several subsidiary centres from which cholera is capable of originating In India there is apparently another endemic centre in central and south Madras The frequent outbreaks that occur in China only a few of which could be traced to India make it certain that there are endemic areas in that country, but these appear to be confined to the Yangtse valley Recent investigations have suggested that there are endemic areas in Burma and the Philippines, but Indo China and Thailand which were at one time under suspicion have recently been exonerated

In Bengal the endemic area is not as extensive as was previously supposed and to date only the districts of Khulna 24 Parganas Midnapore Howrah Hooghly Bankura and Birbhum are definitely known to be endemic These districts are all located on the banks of the Hooghly river The criteria of endemicity that the sanitarians have adopted are — that in a period of 32 years cholera should not have been absent for more


Figure 117

It should be appreciated that in any particular year the incidence of cholera in an epidemic area may far exceed that in the endemic area from which the infection originated

The origin and maintenance of infection — Cholera is an eminently preventable disease because as far as is known the origin of infection is invariably a human being Although the alliterative trinity, the case the contact and the carrier is always menti the tenets of belief of the sanitarian they are not in fact three but one source for the contact is a sub clinical case of cholera carrier is only a prolonged one There is no known animal source tion and the true vibrio has not been isolated from any natural s the absence of cholera for more than a few weeks

The maintenance of the infection in the endemic areas has interested bacteriologists and epidemiologists survival and multi in village water supplies for many weeks is possible (*vide supra*) present opinion is that there is no other residual source of infectio endemic areas except cases and that infection is maintained m *case to case* passage of virulent non hæmolytic O sub group I vib the vast majority of the villages in the endemic areas the sanitat the most primitive nature there are no latrines and no protecte supply The people use the open fields and frequently the banks of (reservoirs) for defæcating Open tanks are their only water sup they will bathe in the tanks wash out their mouths and even d water at the same time

a week or so

In India —With the very great increase in facilities for tra chances of spread of cholera from the endemic areas to other India are considerable but it has been found that normal railwa on business or pleasure does not tend to spread the disease to an

that, though the sanitary arrangements are far from perfect, especially the small stations, there are latrines and a safe water supply Such travell

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poor, and such money and food as they have when they leave their hom are soon finished, so that they arrive in an ill-nourished and exhausted sta Further, it is difficult to make satisfactory sanitary arrangements for t literal millions that attend some of these *melas*, *e g* the Kumbh mela Hardwar, at which the attendance has been estimated at over a million certain days Those pilgrims

who travel through such areas

widely amongst other pilgrims

with them, and, returning to

o As recently as 1930, an epidem

d the United and Central Provinc

le India has in recent years bee almost entirely by the *sea routes, and with improved port sanitation an*

on has been largely controlled Het

infection being carried back to the countries would be considerable unle *special precautions were taken*

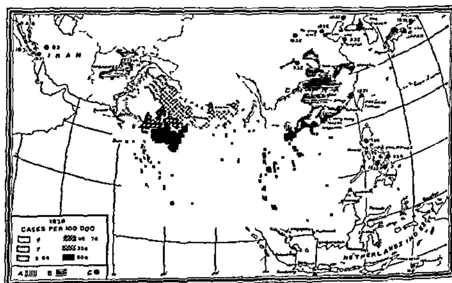


Figure 118 Geographical distribution of Cholera in Asia, 1930–1938 (*League o Nations Weekly Epidemiological Record*)
A Disease reported in 1937 B Disease reported in 1938
C The dates shown on the map for the various territories correspond to those of the latest occurrence of the disease

Climate and cholera —The importance of climate in determining cholera endemicity is obvious from the similarity of the climates in all the

ture appears to be less important in this respect for cholera spreads rapidly in cold countries Attempts to delimit the endemic areas on climatic criteria alone have not been entirely successful Rogers' criterion of an absolute humidity of 0 400 inches of vapour pressure throughout the year can be accepted only in that this constant high humidity is a common feature of all the true endemic areas but it is not correct to suggest that all areas with this degree of humidity are endemic areas even in India

Seasonal incidence —The factors that determine this are different in the endemic and epidemic areas

In the **endemic areas** temperature and absolute humidity are the main

obviously some other factor also comes into operation for cholera incidence declines this other factor is probably the mechanical flushing of contaminated water supplies and the alteration in their chemical and physical character Cholera incidence shows a rise in October as the monsoon subsides and it falls again at the end of the year when temperature and both relative and absolute humidity fall

In the **epidemic areas** on the other hand the cholera incidence curve follows the absolute humidity curve throughout the year reaching its peak in the monsoon months July to October (figure 117)

Variations from year to year forecasts —In both the endemic and

by an epidemic in the next year and after two such successive failures an epidemic is even more certain

The importance to the local sanitary staff of knowing what the chances are of cholera occurring in the epidemic areas or of the incidence being abnormally high in the endemic areas is obvious and has led to a very serious study being made of the cyclical incidence of cholera and of the climatic and other factors that influence it A number of methods of forecasting have been devised but on the whole Rogers (1933) method has

sub endemic areas in Bengal The subject however is too technical to be

undertaken by the average practitioner, as well as being outside his sphere (Russell, 1925, Lal, Raja and Swaroop, 1941)

The natural subsidence of an epidemic—This may be due to the fa… limate, to some change in the water-supply … he exhaustion of one water-supply or the … cause, or to the exhaustion of the clinical material It has also been claimed that it is effected by the development of bacteriophage in the water supply

Towards the end of an epidemic there is usually a decrease in the severity of the disease and a lowering of the mortality

Race, sex, and age distribution—There appears to be little difference in the susceptibilities of the different racial elements in the population and, even in the highly endemic areas, the indigenous inhabitants are very susceptible Men are said to be more frequently affected than women, but it seems possible that there has been a selective tendency in the data on which the statement is based There are also relatively fewer children than adults amongst hospital patients admitted with cholera, but children are susceptible, and in them the disease will usually run a severe course, an infant aged two months with cholera was recently admitted to a Calcutta hospital

PATHOLOGY

Pathogenesis.—The vibrios do not invade the tissues, and do not apparently produce any exotoxin The endotoxin that results from the death and destructio…
dation of the…
great outpouri…
the tissues and blood The tissue changes observed are usually attributed to the absorption of this toxin, but could probably be explained by the dehydration of the tissues themselves and by the hæmo concentration and low blood pressure which results in temporary ischæmia

Morbid anatomy.—The body is dehydrated, though usually well nourished as the illness is a short one There is marked early post-mortem rigidity, in some cases the stiffening of the limbs is almost ante-mortem The muscles are dehydrated, dark red, and firm, and show curious post mortem contractions which in some cases are so marked that they have been known to cause a body to fall off the post mortem table

In the abdominal cavity the omentum will be found as a sticky curled-up mass, the serosa, especially of the stomach, duodenum and small intestine, are pink, the lymph follicles are slightly enlarged, and the contents of the bowel are the typical rice watery alkaline fluid in which there are flakes of mucus and sometimes streaks of blood The mucous membrane of the stomach the small intestine and often the large intestine are congested and there may be petechial hæmorrhages

The **liver** is congested and full of dark viscid blood, there may be some toxic degenerative changes in the parenchyma cells, especially if death took place in the later stages The gall-bladder is full and the viscid bile will not pass along the ducts even when the gall bladder is squeezed The **spleen** is usually small and contracted The **pericardium** often shows petechial hæmorrhages, the right heart and the large veins are full of dark tarry blood The **lungs** are usually shrunken and anæmic, but, if death occurs in the later stages especially when the intravenous saline therapy has failed, they may be œdematous

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The kidney changes are more in the nature of a nephrosis than a nephritis and

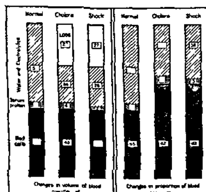
changes in any of the organs and in others in one or two organs only the most constant changes are those due to dehydration

The blood —On account of the dehydration there is often a polycythæmia the red cell count not infrequently rising to 7 000 000 per c mm or more There is a disproportionate leucocytosis often up to 20 000 per c mm with a relative large mononuclear increase The red cell volume percentage which is normally 45 to 48 may rise to 65

The sedimentation rate is increased in the majority of cases but not markedly it would appear that there are two opposing influences because it is mainly in the serious cases in which the specific gravity of the blood is high that the sedimentation rate is within normal limits (deMonte and Gupta 1941)

With the suppression of urine the non protein nitrogen and urea are raised considerably but it returns to normal comparatively rapidly usually within a week after the urinary flow has started again

Dehydration —In the severe case of cholera the symptoms are mainly due to dehydration and loss of chlorides and alkalis (*vide supra*) The similarity between a patient with cholera and one in shock



the specific gravity of the blood the

dom higher

Renal failure —It is easy to understand how hæmo concentration circulatory failure through loss of blood volume and some degree of toxic vaso-

inertia

that th

irrever

The urine—The urine, prior to suppression, will be highly coloured

content may be as low as 0 1% This quantity, and its urea content very l concentrate urea During the next fe efficiency of kidney function more urir may rise above normal Subsequently output will increase further and the urea percentage again drop

SYMPTOMATOLOGY

instances of cholera in which es (contact carriers) are im (*vide supra*) From a clini cal point of view cholera infection may produce any one of three types of cholera —

(*a*) *Mild*—choleraic diarrhœa

(*b*) *Typical severe cholera* with purging and vomiting

(*c*) *Cholera sicca*, a comparatively rare, very severe form of cholera in which the toxæmia is extreme, causing paralysis of the bowels so that the patient dies within a few hours after some vomiting but no diarrhœa, the bowels are found distended with rice-watery fluid laden with vibrios

within 24 hours

The **onset** may be with a moderate diarrhœa which develops in severity but it is much more frequently sudden with violent purging and vomiting After the lower bowel has been emptied of fæcal matter at the first few purgings the stool takes on the typical rice-water appearance a non offensive whitish fluid with flakes of mucus and occasionally streaks of blood The diarrhœa is profuse and painless—described alliteratively as pints of pale fluid painlessly pouring away The diarrhœa is shortly followed by profuse watery vomiting This constitutes the **first stage, or stage of copious evacuations,** and its duration will vary inversely with the severity of the symptoms

The patient then passes into the **second stage, the stage of collapse** The purging and vomiting continues the former becoming a continuous process and the latter being uncontrolled and often precipitate The classi cal cholera facies are assumed—the eyes sunken and cheeks hollow the skin cold and clammy to the touch and cyanotic the fingers shrivelled (washer woman s fingers) the voice husky, and the expression anxious, the patient complains of extreme thirst, and becomes very restless, the blood pressure falls and the pulse cannot be felt at the wrist, the surface temperature may be as low as 95°F the rectal temperature at the same time may however

slowly recover But if the algid stage continues for long the stage of

reaction' may be as serious as the earlier stages The usual explanation of this reaction is that the recovery of the circulation means more blood flowing through the intestinal blood vessels, and more absorption of toxins However, if the kidney failure has been long continued and/or there has ... caused by the ischæmia, ... start to flow again, and a ... ases the temperature rises ... *Cholera has been described* ... suppressed in the collapse ... and doubts whether the early rise of temperature that may occur is really part of the cholera syndrome He has seldom seen any febrile reaction in an uncomplicated case that could not be accounted for by the infusion of pyrogen containing saline The charts of ten consecutive cases are shown in figure 120, in one case the rectal temperature was high on admission, but in no case was there any reaction rise Later rises in severe cases are more easily explained

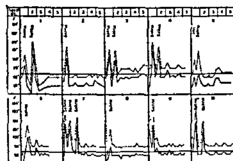


Figure 120 Temperature charts of ten consecutive cases of cholera (broken line = rectal ... was there ... free water

Death may occur in this stage from toxæmia, azotæmia, hyperpyrexia, or from one of the various complications that may appear (*vide infra*) Anuria will usually result in death within four or five days, but there have been instances in which the patient has passed into a semi-comatose state and died on the 9th day of the anuria, recovery has been reported after anuria for four days

The recovery may be temporarily accompanied by the passage of a little concentrated urine with a high percentage of albumin and many hyaline and granular casts, when the blood pressure falls again, the patient will once more become anuric When, however, the patient passes as much as two pints of clear urine in 24 hours, the danger of relapse has usually passed The toxæmia of cholera appears to be comparable to that following ischæmia in crush injury when blood again flows through the injured limb

Convalescence is usually comparatively rapid, but great care should be exercised, as sudden heart failure as the result of slight exertion is not uncommon

Complications.—Enteritis and diarrhœa, pneumonia, parotitis, slough-

DIAGNOSIS

In the large majority of cases, and especially during an epidemic, it will be possible to make a clinical diagnosis with a considerable degree of certainty *In fact, during an epidemic, all suspected cases should be treated* as cholera, and all contacts as potential cases of cholera and as probable

cases of vibrio infection The diagnosis of the isolated case is more important from a public health point of view than from the patient's for when there is severe purging and vomiting with consequent dehydration the intravenous saline treatment is indicated whatever the ætiology

Even without full laboratory facilities, a provisional bacteriological diagnosis can be made by examining wet and dry films under the microscope the latter is made by taking a shred of mucus from the stool, making a *smear on a slide, and staining with weak carbol fuchsin* In the wet film the large number of the organisms, their uniform character, and their very rapid rotatory movements, will lead one to suspect cholera in the stained film the characteristic comma shaped vibrios and their 'fish in stream arrangement will add to the suspicion

Whenever possible the diagnosis should be confirmed by the following bacteriological procedures —

(i) Inoculate several loopfuls of stool into a tube of peptone water (1% peptone 0.5% NaCl adjusted to pH 8 4) incubate for 8 hours take a loopful from the surface and examine fresh and stained If they are gram negative motile vibrios—

(ii) Take a loopful from the peptone culture and streak on (*a*) Vedder and Van Dam (hæmoglobin peptone glycerin and KOH—pH 8 4) (*b*) Dieudonne or (*c*) Aronson plates and incubate for 12 hours Pick out greenish (in *a* and *b*) or red (in *c*) colonies and examine to confirm that they are vibrios

(iii) Carry out a slide agglutination test with standard high titre anti O subgroup I cholera serum to exclude all but the El Tor and the true cholera vibrio

(iv) In order to show whether hæmolytic (El Tor) or nonhæmolytic (true cholera vibrio) to a 5% sheep-blood corpuscular suspension in saline add an equal quantity of vibrio emulsion incubate at 37° C and read after two hours and again after 8 hours

Differential diagnosis —Cholera will have to be distinguished from, amongst others the following conditions —

(*a*) *Fulminant bacillary dysentery*, the diagnosis will be bacteriological but it is unnecessary to wait for this, as intravenous saline treatment is indicated in either case, though in a case of Shiga dysentery the early administration of anti serum would probably improve the prognosis

(*b*) *The algid and choleraic forms of malaria* the differential diagnosis here is very important for though the administration of intravenous saline would do the malaria patient no harm and probably some good the withholding of specific anti malarial treatment might easily be fatal, if there is any doubt a blood film should be examined immediately

(*c*) *Trichinosis* the acute gastro intestinal onset of a heavy infection of *Trichinella spiralis* may simulate cholera and later the muscular cramps might be a confusing element The exclusion of this diagnosis will be difficult and a positive diagnosis of cholera must be sought This infection however is rare in India, the main home of cholera

(*d*) *Food poisoning*—staphylococcal or streptococcal mushroom etc

(*e*) *Arsenic or antimony*

The distinguishing features of the last two are shown in the table following —

TABLE VI (*Differential diagnosis of cholera*)

	Cholera	Food poisoning	Arsenic (and antimony) Poisoning
Epidemiology	Associated with other cases in neighbourhood	Often single group of persons who shared meal no secondary cases	Often one person only
Incubation	24-72 hours	4-24 hours	½ 2 hours
Onset	With purging	With vomiting	With burning in throat followed by vomiting
Nausea and retching	None	Yes	Yes retching marked
Vomiting	*Precipitate* watery rarely blood Continuous	*Often single severe* vomit mucus blood streaked	*Violent continuous* mucus often freely streaked with blood
Evacuation	Early Continuous pouring out of pints of watery fluid inoffensive	Frequent Usually follows vomiting fæcal *plus* blood and mucus often offensive	Delayed Single massive followed by frequent passing blood and mucus
Tenesmus	None	Yes	Very marked
Abdominal tenderness	None	Marked All over abdomen	Very marked
Dehydration	Very marked	Distinct	Slight
Muscular cramps	Constant and severe	Less constant Extremities only	Severe
Surface temperature	Subnormal	Often up to 100-102°F	Normal or subnormal
Headache	None	Often	Often
Urine	Suppressed	Seldom suppressed	Sometimes suppressed later
Blood	Leucocytosis mononuclear increase	Normal	Slight leucocytosis Normal differential

PREVENTION

Grand strategy—No cholera pandemic has occurred since 1884 and in fact for the last thirty years the disease has been confined to its Asiatic homes and to other Asiatic countries in their immediate vicinity This

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in this country with a view to stamping out the disease in the endemic areas

In 1931, the Indian Research Fund Association made cholera one of their main subjects of research, with some of the results reported above The Indian workers, in collaboration with others in England, established the identity of the true cholera vibrio, showed that the cholera case was the only source of infection, and defined the true endemic areas in India, thereby they opened the way for a definite policy of control This policy,

provinces in which the endemic areas exist

Prevention of epidemic extension—In all countries there are strict ...ted ports, and certain ...*re or less permanently* ...easures taken vary in ... have gone as far as to provide for anal swabs being taken from all the lower-class passengers

Within countries, control measures are more difficult to carry out, and have on the whole been less successful, but during the last few decades special efforts have been made to prevent epidemic extension as a result of religious melas At the sites of these melas, latrine arrangements, anti-fly measures and protected water supplies have been instituted Provision has been made for the immediate treating and isolation of the sick Similar ... points on the roads and railways ...ing the last few years, systematic ...ut Besides these special precau-... height of the epidemic seasons, ...tions for detraining and detaining ...r showing suspicious symptoms ... any village where a case has been ... *disinfection of the water supplies* ...ie whole community undertaken Attempts are also made to control the movement of the population to prevent extension of the epidemic to other villages

In the matter of disinfecting wells, discrimination should be observed and only suspected sources of infection treated at first, for, if all well water is made undrinkable, the inhabitants will be compelled to find other waters which may be even more contaminated *vide infra* chlorination of water supplies

Control in the endemic areas—Here the public health policy to be ... One of the main differences ... be of a permanent nature, ... whole year ... be provided with a protected ...olera could be stamped out (see footnote on water supplies*) ...hough the habit of indiscriminate

*Water su... depth of the water table an... course being ideal Althoug... luce water of greater quanti... nsive and in nearly all part... wells 30 to 150 feet deep, ... vary as it is

defæcation in the open fields around the village that is general in most Indian villages probably helps to spread infection during exacerbations of

[illegible]

[illegible] because [illegible] it may prevent the full development of symptoms, it is unlikely to preclude infection completely such an infection which will result in the passage of virulent vibrios for a few days by an unsuspected individual is a greater source of danger than a frank case of cholera

In [illegible]

allowed to take any food on the premises or to smoke flies should be excluded rigidly from the wards and latrines and all those who come in contact with cholera patients should be inoculated preferably a week or

[illegible]

be used unless it is known to have been made from boiled water and no cut fruit or food cooked the previous night and left standing should be eaten These are the standard rules to avoid bowel disease They should always be

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necessary for the well strainer to be in a sand stratum which is below the water-table height during the dry season The water although hard is usually of high purity

Open wells have a greater yield than shallow tube wells in that they also serve as a reservoir However it is harder to maintain purity even when the wells are protected by a proper apron and parapet wall The purity can be maintained if the well is covered and a pump installed

When the water supply is from a *doba* or stream it must be pumped into a reservoir where proper disinfection can be carried out

There is still a mistaken idea of the danger of sub-soil pollution of a well Nearly all well pollution is from the surface In a limestone formation or where there are fissured rock formations pollution may travel quite long distances but in other formations the extension of pollution from a source depends upon the texture of the soil the height of the water table the slope of the water table and the direction of the flow

The old [illegible]
rare ca[illegible]
United [illegible]
the dr[illegible]
little c[illegible]
planning a latrine it should be below the well The direction of the ground water flow can be roughly estimated by the topography of the ground

followed in the tropics but they must be observed with religious formality during a cholera epidemic There is little danger of direct infection of personal attendants on the sick, provided that they avoid a precipitate vomitus splashing into their faces and never take food on the premises or until they have changed their clothes and washed their hands

Special measures of prevention

Inoculation—Haffkine who was a student of Pasteur carried out experiments in Paris in 1892 and applied them in India He used live avirulent cultures followed by virulent cultures Kolle showed that killed cultures were equally efficacious, and killed cultures have been used since *Cholera vaccine has been used very widely for a quarter of a century* Recent evidence of its value rests mainly on one statistically designed and executed investigation conducted under the auspices of the Indian Research Fund Association (Russell, 1927) The figures were as follows —

	Persons	Cases	Deaths
Two doses of vaccine by injection	8 485	31	2
Three doses of oral vaccine	4 982	18	4
Controls	40,258	711	277

It is usual to give two doses, but in many wholesale inoculation schemes it has only been practicable to give one, and the results have not been much inferior This fact, and the apparent equal success of the oral vaccine, about which many workers are very doubtful, has led the sceptics to question the value of cholera vaccine altogether

The vaccine should be prepared from recently isolated strains of non hæmolytic O sub group-I cholera vibrios The vaccine should be formalin killed and contain 4 000 million organisms per c cm in 0 5% phenol, the usual dose is 1 c cm followed a week later by a second dose of 2 c cm

Immunity is said to last from 3 to 6 months, and there does not appear to be a negative phase

Oral vaccine Besredka's oral bilivaccine has been used more extensively in chol [illegible] s investigated by Russell (*loc* [illegible] *ra*) [illegible] it [illegible] r [illegible] g [illegible] results

Disinfection of water supplies **Chlorination**—For filtered water supplies, the usual rule is one part in five million, that is one part of chlorine, or if the chlorine content of [illegible] 3 parts of bleaching powder, this wo[illegible] per million gallons of water But, [illegible] powder varies from sample to sample and as the chlorine fixing power of different water supplies also varies no rule of thumb can be adopted and the amount to be added must be calculated for each well or cistern

The following is a standard method of calculating the amount of bleaching powder to be added

Three standard solutions made with distilled water are necessary

(a) 1 in 1 000 solution of the bleaching powder to be used
(b) 10 per cent potassium iodide solution
(c) 1 per cent starch solution

The volume of water to be chlorinated must first be ascertained For wells this can be calculated from the depth of the water and the diameter of the well by the formula $\pi r^2 \times$ depth where r is the radius (half the diameter) of the well The capacity of tanks and cisterns is calculated by multiplying the length

by the breadth by the depth of the water One cubic foot of water is equivalent to 6¼ gallons

Example A well is 10 feet deep and has a diameter of 6 feet Therefore it contains $\pi r^2 \times 10 \times 6\frac{1}{4} = \frac{22}{7} \times 9 \times 10 \times \frac{25}{4} = 1768$ gallons

Take five white bowls or flasks and in each place 500 c cm of water to be treated

Stir the mixture in each bowl with a clean glass rod beginning with the bowl containing the least amount of chlorine solution and going to the one containing the next smallest and so on

Allow them to stand for at least an hour Then test for free chlorine by adding to each bowl about 1 c
1 c cm of freshly prepared star
gives a faint blue colour Note
added
of po
figure
the u
the a
alreac

then

In the case of the hypothetical well mentioned above which contained 1768 gallons of water the amount of bleaching powder required would be

$$\frac{1768 \times (18+3)\ lb}{1\,000\,000}$$

$= 0.037128\ lb$

$= 260$ grains (or about 17 grammes)

solutions

The calculation is made as follows

$$\frac{\text{Minimum number of drops of bleaching powder solution added to the first bowl in which the blue colour was distinct}}{\text{Number of drops from the dropper that make a drachm}} \times 0\,44 + 0\,021 = \text{Grains per gallon of water to be treated}$$

Example If the fourth bowl was the first to give the blue colour then

$\frac{4}{?} \times 0\,44 + 0\,021 = 0\,1585$ grains per gallon

$= 158$ grains per 1 000 gallons

or in the case of the example given above

$\frac{1768}{1000} \times 158 = 280$ grains (or about 18 grammes)

present A dilution of 1 in 500 000 which produces a faint purple colour in filtered water kills cholera vibrios in a very short time but it will not kill all coliform organisms even in 24 hours

This dilution is obtained by adding ⅛th grain of permanganate to each gallon of water or roughly one pound to each 50 000 gallons

In our hypothetical well which contained 1 768 gallons the amount of permanganate required would be a little over half an ounce

Neither the permanganate nor the bleaching powder should be thrown into the well, but should be mixed in a bucket, the supernatant fluid being

poured off and renewed until the whole amount has gone into solution. Then, the water in the well should be thoroughly mixed by repeatedly lowering and raising the bucket.

TREATMENT

Historical.—Charms amulets and magic were credited with playing important parts in the treatment of cholera [illegible] 'ill held their
o ties. This is
n loyed by the
p were scarcely
b it appears to
h 1 to 2 grains
e was more
ft utrous acids
quinine, strychnine, arsenic, iron, and in fact almost every drug in the pharmacopœia, and many that were not in it. The multiplicity of drugs suggests very strongly that none was of any real value. Other methods employed were venesection, blistering, cupping, wrapping in cold sheets, hot baths, 'electro-magnetic insulation', and a number of other procedures.

With the advent of bacteriology and Koch's discovery of the vibrio, the intestinal antiseptics naturally had a phase, but the value of none was established.

Saline injections were used nearly a hundred years ago in England. The immediate result was said usually to be good, but as emphasis is laid on the word *immediate*, one must assume that the final results were disappointing and [illegible]

better understood and more promptly put into operation.

Introduction.—Treatment must be considered under three headings:—

A *Specific.*
B *Maintenance of biochemical equilibrium.*
C *Symptomatic.*

Hitherto the failure of specific treatment has led to an emphasis on the other two aspects of treatment. The complete success of efficient biochemical-maintenance treatment in a large percentage of cases indicates that, even in those cases in which the natural immunity fails to prevent the establishment of infection, immunity is rapidly developed and soon over- [illegible] ld
in
h-

A. *Specific treatment.*—There are two objectives:—

(i) **The destruction of the vibrio.**—All the various intestinal antiseptics that have been used in the past have failed to influence the course of the disease in the case of cholera.

The advocates of bacteriophage have claimed an earlier disappearance [illegible]
atment,
mouth
cholera,
n every
two hours, or large doses at longer intervals for at least two days.

The essential-oils mixture that has been advocated by some workers is presumably supposed to act as a disinfectant. The essential-oils mixture consists of:—

℞ Olei caryophilli } ♏ vi
" cajuputi
juniperi
Acidi sulphurici dil ♏ xi
Spiritus ætheris ♏ xxv

Half a drachm of the mixture is given in an ounce of water every 15 minutes, up to a maximum of 16 doses

[illegible]

sixty cases in which this dosage was given, we have lost no case against a death rate of about 6 per cent amongst patients treated with saline infusions only (Napier *et al* in press) Reports from elsewhere have not been so satisfactory

(ii) **The neutralization of the toxin** —No great success has been achieved in this direction Potassium permanganate has been most disappointing in the writer's experience and, in the large doses advocated, it appears to cause gastro-intestinal irritation very frequently It seems very questionable whether its *in vitro* toxin-oxidizing properties are reproduced *in vivo* The dose recommended is two enteric coated pills of 2

[illegible]

are —

(i) *the replacement of fluid*

(ii) *the maintenance of the blood and tissue chlorides at their normal level, and*

(iii) *the counteraction of acidosis*

All three can be achieved by suitable intravenous therapy, for example, by the hypertonic and alkaline saline treatment recommended by Rogers The procedure that he suggested was as follows —

Rogers' treatment—Two solutions are prepared —

(a) the hypertonic saline consisting of

(b) the alkaline saline which is prepared as follows —
sodium chloride—90 grains
pure or distilled water 1 pint

this solution is autoclaved to ensure sterility, and to it is added, from a previously sterilized packet containing the exact amount, 160 grains of bicarbonate of soda*

* Sodium bicarbonate is converted to carbonate if a solution of it is heated for any length of time

He took as his main indication for the giving of intravenous saline the specific gravity of the blood, measured by means of glycerine bottles (*vide supra*) A specific gravity of 1061 he suggested indicated a loss of one pint of fluid, 1062 two pints 1063 three pints and so on Fluid was replaced accordingly, by giving first one pint of alkaline saline and making up the balance with hypertonic saline He recommended giving the intravenous salines at the rate of about a pint in 5 minutes

Rogers' treatment has been the basis of all successful treatments of cholera for the last 25 years During this time many modifications have been introduced and individual workers have naturally interpreted his technique in different ways

Modified procedure — In the cholera wards of the Campbell Hospital in Calcutta the procedure is as given below, this scheme has been worked out by the physicians especially Dr B C Chatterjee, attached to this hospital in conjunction with the cholera research workers at the Calcutta School of Tropical Medicine The following four solutions are made up and kept ready for use They are made with pyrogen-free* sterile distilled water, and the precautions suggested above regarding the sterilization of bicarbonate in the dry state are observed

(*a*) *Hypertonic saline*		
Sodium chloride	140 grains or	16 00 grammes
Pyrogen free distilled water	1 pint	1 litre
(*b*) *Alkaline saline*		
Sodium chloride	80 grains or	9 00 grammes
Sodium bicarbonate	180 grains	20.50
Pyrogen free distilled water	1 pint	1 litre
(*c*) *Alkaline hypotonic saline*		
Sodium chloride	60 grains or	6.80 grammes
Sodium bicarbonate	180	20.50
Pyrogen free distilled water	1 pint	1 litre
(*d*) *Bicarbonate solution* (*5 per cent*)		
Sodium bicarbonate	440 grains or	50 00 grammes
Pyrogen free distilled water	1 pint	1 litre

Indications —Intravenous solutions are given in all severe cases in which there is any evidence of dehydration or if the patient is at all collapsed, if possible, the extent of this dehydration and collapse are

---

* are found in
Subsequent
prepared as

In a clean glass still re-distil some freshly distilled water to which a little sulphuric acid and one or two crystals of potassium permanganate have been added to give it a faint pink colour If during the process of distillation the pink colour disappears from the water in the still a little more sulphuric acid and potassium

is been previously prepared
and sulphuric acid then
gen free water and finally

sterilized by autoclaving

The pyrogen free water is sterilized in an autoclave and may be used for about 3 to 4 days

When distilled water is already available the following method may be adopted to ensure that it is pyrogen free

Add powdered charcoal (B.D.H activated charcoal for preference) to distilled
This is shaken thoroughly for a few
to settle out the supernatant fluid is
ly clean flask or bottle (*vide supra*)
h cotton wool but closed with a glass
and the neck of the receptacle, it must
which it may be stored for a few days
treated again

ascertained by estimating the specific gravity of the blood and taking the blood pressure If ... 80 mm of mercury, or the specific grav ... pints are prescribed, if 1060 to 1062, tw ... 4, up to three pints. It is seldom wise to give more than three pints in the first instance, at any rate in the low-weight type of Indian, but, if circumstances permit, the perfusion should be continued by the drip-feed method

Method —The specific gravity of the blood is estimated under clinical conditions by adding drops of blood to a series of bottles of glycerine diluted with distilled water to make the specific gravities 1050 1052 1054 and so on up to 1070, for practical purposes, it is usually sufficient to have bottles from 1054 to 1064. If the specific gravity of the blood is greater than that of the glycerine in the bottle, the drop will sink if it is less, it will come to the surface The bottles can be used for some time if they are carefully corked if they are not ... and the specific ... rise as a result

... rights pipette ... the bottle of ... will probably ... led drop either ... ific gravity of ... of the blood ... ken as between

... rs, that is, from 24 to 48 hours from the ... ersed and 1 part of hypertonic saline ... After 48 ... most prominent feature, and hypotonic alkaline saline should be given If however the specific gravity of the blood is not much increased but nevertheless the patient is suffering from acidosis, then the bicarbonate solution only is required, and about half a pint of this should be given

It will very often be necessary to repeat the infusions, sometimes as many as half a dozen times, if the fluid evacuation continues if the patient collapses again, or if the dehydration is re established (evidenced by a rise in the blood

... ian ... the ... pro-cedure of running in two pints of hypertonic saline and following this by a pint of plasma to keep it there, *so to speak*, has been adopted in a few cases, apparently with complete success, but, as it will be seen from figure 119, there are not the same indications for giving plasma in cholera as in shock

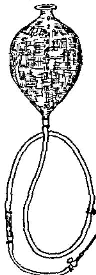


Figure 121 Apparatus for giving saline, with the drip-feed apparatus incorporated in the tube (in this figure the length of the tubing between the drip-feed and the needle is shorter than it would be in practice)

ratus may be interposed a foot below the reservoir,

and 3 inches of glass tubing to act as a 'window' a short way from the lower end At the lower end of the tube, a record needle adapter, preferably with a stop-cock, is inserted, and a serum syringe needle fitted (see figure 121) For giving by the open method the needle
cannula, again preferably
A suitable vein, usually
in front of the

of th ge with the body in
comp pad placed under the
elbo

A sphygmomanometer cuff or a tourniquet is applied to the arm, compression of the deeper arterial supply is avoided, if necessary, the patient should be made to open and close the hand or to bend and extend the elbow, several times in order to fill the veins

The selected area is painted with tincture of iodine and then washed with alcohol Local anæsthesia of the skin may be produced by injecting a few drops
ith a fine hypodermic
st be held firmly so

d with the infusion
expelled The needle
ery acute angle with
into the vein Some
he experienced hand
a sudden failure of
about or just below
ned, blood will flow
into the tube and be visible at the window The tourniquet is now released and the reservoir raised and the flow will be reversed The reservoir should be attached to a stand, about 3 to 4 feet above the level of the patient

A very convenient refinement is a serum syringe with a side nozzle to which the lower end of the tubing from the reservoir is attached the adapter being discarded the needle is attached in the usual position With the aid of this syringe the operator has perfect control of the needle whilst inserting it into the vein The piston is slowly withdrawn when blood will appear The tourniquet is released and the side stop-cock opened to allow the saline to flow



Figure 122 Cannula for inserting into vein

When the veins are collapsed the open method is employed A tourniquet is applied as before Under a local anæsthetic a small incision is made the skin being steadied by the index finger and thumb of the left hand The vein is isolated by forceps dissection The closed forceps or an aneurysm needle are then passed under the vein and a double strand of sterilized catgut is drawn under it The catgut is divided to provide two ligatures The distal piece is drawn down under the exposed vein and is tied the ends being left long The proximal one is drawn up under the vein to the upper end of the wound

The fluid
The vein being
fine scissors
knotted and
is then started

When the infusion is completed the cannula is withdrawn but the ligature

used again

Rate and temperature of administration—At first, while the patient is pulseless, the infusion can be given briskly, at about 4 ounces per minute,

* As bicarbonate solution will cause pain and a sharp local reaction if even a small amount is allowed into the subcutaneous tissues a small amount of isotonic saline should always be placed in the reservoir first, until the cannula is *in situ* and a satisfactory flow has started

be met by reducing the rate of flow rather than by abandoning the procedure After three pints have been given, the infusion may be continued at a very much slower rate 40 or even 20 drops per minute (1 pint in four or eight hours)

If the rectal temperature is 101°F or above, all intravenous infusions
reaction possibly ending in hyper-
rature of the fluid must certainly
If the rectal temperature is also
e saline up to body temperature
weather in most endemic areas this
is a very unnecessary complication of administration

Other routes of administration —In children and when it is not possible to find a vein, hypertonic saline may be administered subcutaneously, intramuscularly, into the sternum or tibia or into the peritoneal cavity, alkaline saline cannot be given by these routes In mild cases alkaline isotonic saline can be given per rectum but if there is much purging little will be absorbed After administration of salines intraperitoneally the foot of the bed must be raised as the absorption from the pelvic peritoneum is very poor

C. *Symptomatic treatment* —The intravenous therapy will play an all-important part in the treatment and prevention of collapse and of many other serious complications such as anuria but other measures may also have to be adopted

Collapse and shock —The administration of atropine sulphate 1/75th grain when the patient is first seen to be repeated after about 12 hours if the patient is still collapsed was first suggested by Lauder Brunton and is recommended by Rogers Atropine reduces all secretions, except renal secretion it therefore helps to conserve fluid and at the same time to reduce the tendency to œdema of the lung when saline is given It also reduces irregular peristalsis, and is a cardiac stimulant This appears to have some effect in reducing the shock Pitressin 1 c cm (pituitary extract —posterior lobe) or, if not available desoxycorticosterone acetate 20 c cm (synthetic suprarenal cortical extract) will often help towards the recovery of the pulse during the collapse stage Other routine measures for the treatment of shock, hot water bottles, massage etc may have to be resorted to

Anuria —With the recovery of the blood pressure the kidneys will usually start to secrete urine again but if hypertonic saline alkaline saline, bicarbonate solution, and injections of pitressin and desoxycorticosterone acetate fail, glucose 5 per cent (1 pint), intravenously strophanthin gr 1/100, caffeine and sodium benzoate gr ix intramuscularly hot fomentations to the loins, dry cupping, hot colonic washes intravenous sodium sulphate (1 89 per cent) by the drip-feed method and finally distension of the bladder with warm citrate saline (2 per cent citrate in normal saline) should be t...

be repeated

In the reset on
very ould be treated

often ring, this will
to ¼ gr doses
of calomel repeated at half-hour intervals up to six doses, followed by a dose of bismuth salicylate The following prescription will be found useful —

℞ Calomel	gr ¼
Chloretone	gr 2
Menthol	gr ½
Sodium bicarbonate	gr 2½

Muscular cramps should respond to the hypertonic saline treatment, but, if they persist and are very painful, self-administered whiffs of chloroform will often meet the case

Morphia and alcohol should be avoided at all stages of the disease *Rogers considered that the early administration of morphia definitely affected the later prognosis, making both suppression and acidosis much more likely to occur*

a mi
flavo
wate
stomach or the rectum, it should be given intravenously as a 5 per cent solution, up to a pint

Later, arrowroot, albumin water, milk whey, milk, fruit juices, meat

so, the patient may be allowed to return to a full diet
save the patient from exhaus-

great care must be taken not to allow
as sudden heart failure is not uncor
valescence is very rapid, once the acute symptoms have subsided

Summary of treatment —The fate of the patient will depend on the skill of the physician, on the facilities that the latter has at his disposal, and on the energy that he devotes to the case Of the 'specific' treatments

given The symptomatic treatment must be given as the condition of the patient indicates Convalescence should not be hurried

Some reported results —In 1936 Pasricha, deMonte and O Flynn carried out a large series of treatments to appraise the value of cholera-phage in the treatment of cholera, the crude results were as follows —

	Treated with 'phage	Treated without phage
Total number of cases	684	685
Total deaths	92	114
Percentage mortality	13.5	16 6

Further analysis of the data suggested that the difference between the phage treated cases and the others was greater than the crude figures indicated

In a second series three years later Pasricha deMonte Chatterjee and Mian (1939) compared a number of forms of treatment After excluding all patients who died within three hours of admission and the very old and very young the results were as follows —

Treatment	Number of patients	Number of deaths	Percentage mortality
Calomel	75	9	12 0
Potassium permanganate	35	4	10.8
Essential oils	46	4	8 7
Sulphapyridine	43	4	9 3
Choleraphage	43	1	2.3
	244	22	9 0

In this series the phage was prepared by a different method The cases were taken strictly in rotation but by a mistake two patients were put on calomel to each one put on each of the other treatments

In 1941 Chopra deMonte Gupta and Chatterjee reported the results of treatment with small doses of sulphanilyl guanidine as follows —

	Number of patients	Number of deaths	Percentage mortality
Sulphanilyl guanidine	468	26	5.56
Controls	87	6	6 90

[illegible]

covery rate was higher with the large dosage

Conclusion —In all these series *all* the patients were subjected to the routine saline infusion treatment The results appear to indicate that choleraphage has a definite beneficial effect They also indicate a progressive improvement in the routine treatment for cholera in the hospital in which this was carried out or possibly a decrease in the virulence of the disease there is little external evidence to support the latter interpretation

PROGNOSIS

This is intimately associated with treatment and the reader is referred to the previous paragraphs

[illegible]

sub-ideal hospital conditions at the present day, it is seldom above 10 per cent It must be remembered that results of treatment in hospital will *always* be better than in the 'field', because, in the worst cases death occurs before the patient can reach hospital, and therefore not only are conditions better, but the population is a selected one In cholera epidemics it is usually found that the death rate is much higher at the beginning than at the end of the epidemic

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BACILLARY DYSENTERY

and adult diarrhœa in temperate countries

(iv) Other rarer organisms, e g *Bacterium ambiguum* Schmitz, an organisms of doubtful pathogenicity, e g *Proteus morgani*, *Bacterium alkalescens*

[illegible]

table VII

Resistance.—Dysentery bacilli are killed at a temperature of 55°C in one hour, by 0 5 per cent phenol in 6 hours, and by 1 per cent phenol in [illegible] for 20 to 25 da s They survive in wa [illegible] ive for 17 [illegible] days

TABLE VII

Shows sugar reactions of dysentery bacilli (after Topley and Wilson, 1936)

	Glucose	Mannitol	Lactose	Saccharose	Dulcitol	Rhamnose	Sorbitol	Litmus milk	Indole
Bact dysenteriæ Shiga	A	—	—	—	—	—	—	sl A	—
Bact ambiguum Schmitz	A	—	—	—	—	A	A ∓	sl A	+
Newcastle bacillus	A g	A (g)	—	—	A (g)		—	sl A sl alk	—
Bact dysenteriæ Flexner	A	A	—	A ∓	—	A ∓	A ±	sl A sl alk	±
Bact sonnei	A	A	(A)	(A)	—	A	A	A (clot)	—
Bact alkalescens	A	A	—	—	A	A	A	alk	+
Proteus morgani	A	—	—	—	—	.	.	N alk	+

A = acid
alk = alkaline
g = a little gas

± = sometimes
∓ = usually
sl = slight
Brackets indicate late formation

All are non motile except *Proteus morgani* and possibly the Newcastle bacillus all reduce nitrates to nitrites and are Voges Proskauer negative

group and Sonne bacilli injected into laboratory animals are toxic, but only in much larger doses (about 20 times) than in the case of the Shiga organism They do not give rise to very efficient antitoxic sera

Distribution in the body and the recovery of the organism —The

only 6 per cent during the third five days With the new media now in use, much higher percentages should be obtained The organisms are never isolated from the blood or urine

Carriers —It is not uncommon for a patient to continue to pass dysentery bacilli for a considerable time after the acute symptoms have subsided In one large scale investigation during the 1914–18 war, it was shown that 7 59 per cent of patients became carriers and that 2 78 per cent were 'persistent' carriers, that is, they continued to pass bacilli for three months or more
the carrier state
regularly, whereas
for two or three
passing bacilli fo
transient

New media (*vide infra*) for the isolation of dysentery bacilli have thrown new light on the carrier problem, particularly with regard to the symptomless (or contact) carrier
it has been shown that ratio of
carriers is on the average 1 to 3
7 in the case of Flexner infections
tions

European countries are usually traced to a carrier employed in the preparation of food but in the tropics while flies are probably the commonest agents of infection, a number of epidemics have been traced to unsatisfactory water supplies

Routes of invasion —Invasion is always by the oral route As in cholera, low gastric acidity probably helps to allow the bacilli to pass through the stomach and invade the bowel

IMMUNOLOGY

Antigenic structure.—The antigenic structure of the dysentery bacilli is an interesting study; that of the Shiga bacillus is homogeneous, and, though there is some cross-agglutination between it and the Schmitz bacillus, there is no cross-absorption The Sonne bacillus is also homogeneous and distinct, but " [illegible] is heterogeneous, there are at [illegible] ch are capable of making a co [illegible] are however six main antigen[illegible] types now recognized, three of the original five Andrewes types, V, W, and Z, and Boyd's 103, P119, and 88, the last probably being identical with the 'Newcastle' bacillus which shows rather different biochemical reactions from the other members of the Flexner group (the X type of Andrewes seems to have disappeared). The polyvalent Flexner agglutinating sera are issued by the Standards Laboratory, Oxford; no I will agglutinate types V, W, and Z, and is practically identical with the [illegible] and Russell, [illegible] agglutinating [illegible] pathogenic types, and monovalent sera have been prepared for three types now designated *Bact dysenteriæ* Boyd, 170, P288, and D1

Agglutinins.—These appear in the blood between the 6th and 12th days of the disease, but the titre declines rapidly after convalescence, and has often returned to normal levels at the end of three months In a normal individual, the Shiga titre may be as high as 1 in 20, and in an infected [illegible] and the normal person may show an agglutination of 1 in 50

Immunity.—There is little evidence of the existence of any natural [illegible]

Little success has attended attempts to produce active immunity by inoculation, and, though vaccines are used in treatment, especially of chronic Flexner dysentery—the Shiga organism being too toxic—any good results that have followed are probably due to the non-specific action of the vaccines Passive immunity that lasts a few months can be produced by means of anti-serum in the case of Shiga dysentery, but it is not a practical measure The antitoxic value of this anti-serum is however very well established (*vide infra*)

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* In a recent paper Boyd (1940) has attempted to simplify the classification of the large (and enlarging) Flexner (mannitol-fermenting) group His proposal which is receiving general acceptance, at least in the British army, is as follows —

Name		Old name
B dysenteriæ Flexner	I	Andrewes and Inman V
,, ,,	II	,, ,, ,, W
,, ,,	III	,, ,, ,, Z
,, ,,	IV	Type 103
,, ,,	V	,, P119
,, ,,	VI	88-Newcastle-Manchester group
B dysenteriæ Boyd	I	Type 170
,, ,,	II	,, P288
,, ,,	III	,, D1

PATHOLOGY

Morbid anatomy.—Except that in the acute toxæmic cases there is marked congestion of the solid organs, especially the liver, kidneys and suprarenals in which there may be some toxic necrosis of the parenchyma cells, the lesions are confined entirely to the large bowel, the ileo-cæcal valve, and the last few feet of the small intestine beyond congestion there is usually little evidence of the disease on the peritoneal surface of the intestine, except possibly in the chronic ulcerative stage where there may

o severe Flexner infection, the following pictures may be encountered (i) In a very severe case where the toxæmia was intense and death occurred early, the whole or a greater part of the large intestine and lower end of the ileum is lined with a white or yellow (bile-tinged), fibrinous membrane, suggestive of a diphtheritic membrane (ii) When death occurs at a slightly later stage in an acute attack, the mucous membrane is intensely red, and is covered by strips of dark greenish-grey necrosed mucous membrane, that are separating particularly along the tops of the ridges of the mucous membrane It is possible, if great care is exercised to see the

on account of the congestion and œdema of the surrounding mucous membrane The ulcers are usually but not always transverse they are irregularly

but it shows a *tendency to heal* *The condition is well seen by means of*

cases come to the post-mortem table but this condition can be seen with the sigmoidoscope

Sites of the lesions.—In severe attacks the whole extent of the large bowel and the last few feet of ileum are involved however the

tion and thickening of the mucous membrane, with œdema polymorphonuclear infiltration, minute hæmorrhages, and a considerable amount of

mucus and sometimes a little fibrinous exudation In the severer forms, there is an extension of the inflammatory processes to the submucosa, where the lymph follicles are the most important centres of inflammatory activity There is in these cases considerable thickening of both the mucous and submucous layers, the inflammatory œdema leads to thrombosis of the veins with numerous hæmorrhages in the submucosa, and coagulation necrosis causes the death and separation of the mucous membrane There is sometimes a certain amount of round-celled infiltration of the superficial muscular layers, but the deeper layers and the serous coat are practically never involved With the loss of the mucous membrane, there is forma

d new blood vessels
columnar epithelial
ulcer During the

inflammatory processes, even if the mucosa is not destroyed altogether,

normal bowel content will be emptied, after this the patient passes very little fæcal matter, but a whitish gelatinous mucus flecked with blood, and later, bright-red gelatinous mucus, which has exactly the appearance of red-currant jelly, is very viscid and adheres to the bed-pan, in a back ground of brown watery fluid The stool has an albuminous smell and an alkaline reaction

Microscopically it is a very cellular picture, with very few bacilli and little debris to be seen, the cells are (*a*) polymorphonuclears showing little degenerative change, (*b*) red cells lying singly or in small rouleau

Blood picture—There is nearly always a slight but distinct leucocytosis, which does not however usually rise above 15 000 per c mm, there is a relative increase in polymorphonuclears This leucocytosis is absent in the later stages, and there may even be a slight leucopenia In the acute choleraic attacks of Shig
account of the fluid loss
the later stages, there is
In chronic dysentery there is very frequently a macrocytic anæmia of nutritional origin

SYMPTOMATOLOGY

The clinical attacks caused by the specific dysentery organisms vary from a mild diarrhœa, in which the patient is scarcely inconvenienced at all, to a very severe toxæmic attack which simulates a severe attack of cholera, in neither of these extreme cases does the true dysentery picture appear The fully developed syndrome also shows a wide range of variations, from the case in which blood and mucus are passed for a few

collapse

in contrast to the incubation period in amœbic infection which is often very long

other symptom, hich is also very

with fever and continuous dysenteric stools which, even if the patient recovers eventually, will lead to a chronic dysenteric condition with

will depend on the virulence of the organism, the resistance of the patient, and the treatment given

In severe Shiga infections, the onset may be with a mild diarrhœa and very little fever, the condition becomes rapidly worse, with the development of fever and the passage of innumerable stools consisting of pure blood and mucus, exhaustion follows rapidly, and early death occurs. On the other hand, the symptoms may be mainly due to the toxic action of this organism cyanosis and later extreme pallor, a fall of blood pressure abatement or disappearance of abdominal pain and tenesmus, the passage of *profuse watery stools, and vomiting, or sometimes abdominal distension and/or acute dilatation of the stomach, conditions suggesting cholera* of

—and at some subsequent date a relapse, which may be much more severe than the original attack, may be precipitated by some secondary factor,

ie very acute attack with

æmia, and death in a few *days, and for the choleraic type, no further description is needed than the* statement that the attack simulates cholera (*q v*) In the typhoid type, after the acute dysenteric symptoms have subsided, the general condition of the patient does not improve, the temperature continues, and a toxæmic state develops

Recurring, or relapsing bacillary dysentery.—It is very often the experience of new arrivals in a tropical country that they suffer a succession of mild attacks of dysentery, which keep them in a continual state of subhealth, for a period of a year or more If none of these attacks has been very … and possibly suffer no furth … n in the country … *rather than relapsing* dysentery, as they are almost certainly examples of reinfection with *different strains of dysentery bacilli, which continue until the* individual has acquired a specific immunity to all the common local strains, or a group immunity that is sufficiently well developed to afford protection against all allied dysenteric strains If a careful bacteriological examination is carried out, it will usually be possible to isolate a Flexner-group bacillus, or more rarely an organism of one of the other species, on each occasion

Those who are less fortunate will include in their early experiences one or more attacks of a much more severe kind, which will leave their *bowel mucosa considerably damaged so that it is never quite one-hundred-*per-cent functionally efficient, and possibly with a number of healed ulcers, the ba … thin layer of mucous membrane over scar ti … ak down under any adverse dietetic circum … often never have a really formed stool, … two loose stools, but for the rest of the day they may have no further trouble In these cases, the main dysfunction appears to be failure of absorption in the lower bowel Periodically, as the result of a chill a dietetic indiscretion, or some other cause they will have a *relatively m* … condition with the passage of mucus but pro and perhaps mild constitutional sy *these occasions dysentery* organism this is certainly not the rule, and

patients who are incidentally carriers that the dysentery organisms are recovered [illegible] this condition is really accident[illegible] cause These cases are usually [illegible] but they are really mild forms of

Chronic (bacillary) dysentery —The distinction between this group [illegible]

knees, ankles, wrists, elbows, fingers occasionally the sterno-clavicular and [illegible] nts One characteristic is the habit of flitting from joint to [illegible] aries in different localities, and In some places it is rare, and [illegible] atients The pain is out of proportion to the redness and swelling which may be very slight On the other hand **hydrarthrosis** especially of the knee joints is not uncommon The fluid is usually sterile but contains the specific dysentery agglutinins, often in relatively high titre

Arthritis usually appears within the first few weeks of the attack, but on some occasions the onset is postponed for as long as three months The cond[illegible]

[illegible] cyclitis, or anterior uveitis coming on during convalescence There is marked tenderness photophobia, and blepharospasm

Acute parotitis is not uncommon and in some epidemics an acute suppurative parotitis has been described

Intussusception is not uncommon in children and a lookout for a [illegible] ion should be kept [illegible] r bacillary dysentery to [illegible] affected there being loss [illegible] cular spasms and cramps, [illegible] condition persisting for a month or so

Nutritional disorders —[illegible]

ascite[illegible]
perit[illegible]
stem[illegible]
order[illegible]
bowe[illegible]

be an indirect sequel due to liver damage Napier and Neal Edwards (1941) considered that there was an association between macrocytic anæmia in pregnancy and bowel disorders, and the writer (Napier, 1939) has frequently associated nutritional macrocytic anæmia with diarrhœa and dysentery

Terminal —The patient with relapsing dysentery who does not receive appropriate treatment, or who fails to respond to treatment, will usually die of exhaustion and asthenia, but pneumonia as a terminal event is not uncommon in cold climates

DIAGNOSIS

[illegible]
any [illegible]
treat [illegible]
and [illegible]
shiga [illegible]
betw [illegible]
cated [illegible]
alway [illegible]
and [illegible] dysentery is given at the end of this section

The milder forms of bacillary dysentery may be difficult to distinguish from ordinary digestive upsets, and the fulminant choleraic type from true cholera In view of the possibilities of more serious development an accurate diagnosis in the milder types is important to the patient himself, and, from a public health point of view, as a signal to tighten up all sanitary precautions, it is even more important that the true nature of such an infection should be revealed In the choleraic attack of dysentery, the immediate treatment is practically the same as for true cholera (intra [illegible]

[illegible]
public health poin[illegible] nt
of the far greater [illegible]

Stool examir[illegible] ve
very valuable information In Mesopotamia during the 1914–18 war, the writer knew a competent pathologist who claimed that he could make as accurate a diagnosis by inspection and a piece of litmus paper as with a microscope, however, he only adopted the procedure during the worst rush periods

[illegible]

Bacteriological examination —The two most important points for the [illegible]

The sequence is so often as follows —In the case of a sub acute attack the physician is not called in for the first few days, he then calls at the patient's house and makes a provisional diagnosis of dysentery, but the patient has not

mucus a loopful of fluid stool should be stroked across the plate or tubes *

---

* There are several new select ve med a on wh ch the growth of the ord nary saprophytic organisms in the stools is inh b ted so that the pathogen c organisms grow and are eas ly identified A good example of such a med um is SS (Sh gella Salmonella) agar the compos tion of which is as follows —

Bacto beef extract	5 0 grammes
Proteose peptone	5 0
Bacto lactose	10 0
Bacto b le salts no 3	8.5
Sod um c trate	8.5
th osulphate	8.5
Ferric c trate	1 0 gramme
Bacto agar	17 0 grammes
Bacto neutral red	0 025 gramme

To prepare the med um for use suspend 63.5 grammes in 1,000 c cm of cold dist lled water Boil for a minute or two to d sol e the med um completely Do

med um and prepared a med um wh ch also unfortunately has many fore gn ingred ents In the writer s personal exper ence very good results have been obta ned with this med um in enter c dysentery and cholera cases

The const tuents are —

Lemco (Oxo Ltd)	0.50 per cent
Peptone (Difco)	0.50
Sod um taurocholate	0.85 "
c trate (Merck)	0.80 "
th osulphate (Merck)	0.85 "
phosphate (Merck)	0.75 " "
Ferr c c trate	0.30 " "
Lactose (Merck)	0.25 "
Agar	2.50
Neutral red 0.25 per cent (Grubler and Co)	1.5 c cm to 100 c cm

Stock agar prepared from Lemco peptone b le salts and agar 7.0 pH is kept ready in 100 c cm quantit es This is melted and to it sod um c trate sod um thiosulphate ferric c trate and ne tral red in the requis te quant ties are added

Sod m hydrox de (2 N) 0.5 c cm is then added to make the final pH 7.4 the medium is then bo led for two m nutes and poured into plates

These media should be inoculated heav ly w th a generous sample of stool

As has been indicated above, the percentage of positive findings will vary considerably in different circumstances, and will depend on the nature of the stools and the stage of the disease (see p 403)

Serum agglutination —Though suggestive agglutinations will often be obtained (*vide supra*), this method is of little practical value in the diagnosis of bacillary dysentery, on account of the late development and the relatively low titre of the agglutinins, even as a measure of retrospective diagnosis, its value is limited on account of the early decline of the agglutinins

sigmoidoscopy is not only extremely painful, but may be dangerous in the very acute stages of the disease In the ordinary acute, in the sub acute, and in the chronic types, it may be very valuable as a diagnostic procedure, a guide to treatment, and an indicator of progress under treatment The [illegible] and the stage [illegible]

by taking swab specimens directly from the ulcerated surface and examining them

In an acute or sub-acute dysentery in which blood and mucus is being passed, if there is no general inflammation of the mucous membrane, bacillary dysentery can usually be excluded, and a diagnosis of amœbic dysentery made

Technique —In [illegible] s inadvisable to prescribe a [illegible] en on the previous night and [illegible] hould be followed by an al[illegible] iema and washout should not be retained and the patient must be encouraged to pass them by gentle exercise if possible Nervous or sensitive patients should be given [illegible] position of the [illegible] haps the most [illegible] e of a proper [illegible] ies face down [illegible] are in the air [illegible] inches in the [illegible] inserted and [illegible] guidance with [illegible] mbrane comes into the field it is examined, [illegible] me to remove mucus by gentle swabbing The instrument must only be advanced when the operator can see a clear passage which will often have to be created by gentle inflation By means of sterile swabs specimens can be taken directly from the ulcers for culture and/or microscopical examination

PREVENTION

The application of the general principles of sanitation, especially with reference to water supply, food, fæces disposal, and flies, is the only real

TABLE VIII

Contrasting bacillary and amœbic dysentery

	Bacillary dysentery	Amœbic dysentery
EPIDEMIOLOGY	Epidemic in temperate climates endemic and epidemic in tropics Common in children	Endemic and rarely epidemic mainly tropical Less frequent in children
PATHOLOGY *Bowel*	Depressed serpiginous ulcers often transverse in thickened and inflamed mucous membrane Sigmoid and rectum mainly also lower end ileum	Deep oval or round ulcers with raised undermined edges in healthy mucous membrane all layers affected cæcum and flexures never ileum
Stools	Very frequent scanty viscid mucus non-offensive bright red blood or red currant jelly Alkaline Very cellular polymorphs (not degenerated) columnar epithelial cells and macrophages RBCs discrete	Less frequent fæcal bulky, offensive dark blood and mucus or anchovy sauce Acid Not very cellular degenerated lymphocytes clumped RBCs Charcot Leyden crystals active amœbæ containing red cells
Blood	Leucocytosis only in acute stages subsequently normal or leucopenia	Usually leucocytosis increases with liver abscess
SYMPTOMATOLOGY *Incubation*	A week or less	A fortnight to many months
Onset	Acute	More often insidious
Fever	Usual	Rare
Abdominal pain and tenderness	Severe localizing to left side	Variable may be severe localizing to right side
Tenesmus	Usually severe	Less severe often absent
Terminal	Toxæmia and exhaustion	Exhaustion and complications
Complications and sequelæ	Few polyarthritis	Peritonitis and hæmorrhage hepatitis and liver abscess common Multifarious sequelæ
SIGMOIDOSCOPY	Not good practice in acute stages red inflamed mucous membrane readily bleeds rigid bowel wall ulcers seldom seen	Permissible in sub-acute attack raised button like ulcers or numerous minute ulcers (mouse-eaten appearance) with red edges in normal mucous membrane
THERAPEUTIC TEST	No response to emetine	Marked improvement with three 1-grain doses emetine on three successive days

preventive measure A marked fall in the incidence of dysentery in a community such as a tea garden labour force follows the introduction of protected water supply a further reduction almost to the point of limination will be achieved by the establishment of a satisfactory latrine stem when this is possible In institutions and other communities which ave common feeding arrangements a careful search for carriers should made amongst food handlers, and dysentery convalescents should not be ployed in this capacity at least for many months and after repeated cteriological examinations

There is no evidence that prophylactic inoculation is of any value

RURAL SANITATION

Rural water supplies and water disinfection have been discussed above (p 386) reference to rural sanitation would perhaps be appropriate here

Rural sanitation, particularly in India is not a problem that is likely to be olved by any single formula the conditions are far too varied However the

one recent advance in sanitary engineering that has come nearest to providing this solution is the bored hole latrine Notes on this subject, kindly given to me by Mr B R Dyer, professor of sanitary engineering at the All India Institute of [illegible] by Mr G Ghosh (1942) of [illegible]

[illegible]

the flow

The advantage of the bored hole latrine is that it is easy to install and very cheap, having a small diameter, the fæces are incorporated quickly in the soil in the bored hole There is no smell when the surface of the content of the latrine is more than 3 feet from the ground surface and there is no breeding of flies It [illegible] months after a bored hole latrine has been [illegible] the soil *The life of a bored hole latrine* [illegible] year after the hole has been filled to [illegible] and abandoned, the squatting plate and the superstructure can be moved to another site

Construction —The bored-hole latrine is a round hole bored into the earth with special auger *16 inches in diameter The depth to which it is bored depends on* the sub-soil water level There should be a minimum of about 3 feet of water during the dry season

A hole about 6 inches deep and 16 inches in diameter is first dug and the [illegible] When the auger [illegible] put back into the [illegible] hed [illegible] n be protected by [illegible]

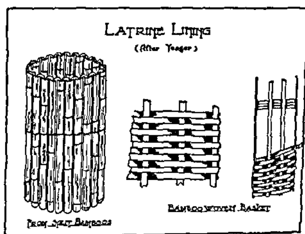


Figure 125

Squatting plate.—This should be of reinforced concrete Squatting plates 3 feet by 2 feet 6 inches are made of cement concrete in the following proportions cement 1 part, sand 2 parts stone or brick chips (¼ inch to ½ inch) 4 parts

The thickness of the plate throughout is 2 inches The plate is sloped 1½ inches from edges to centre The concrete is reinforced with ¼ inch diameter rods (figure 126)

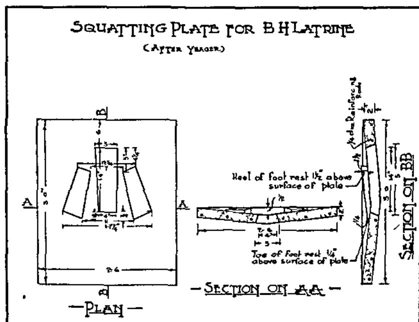


Figure 126

The bare squatting plate with the hole is first cast in a mould After 24 hours it is removed from the mould and the top surface is smoothed and the foot rests are added

It should be noted that the face of the hole in the squatting plate is splayed ... the l... area of the hole on the bottom

... nder water for a ... latrine ... An inexpensive ... bamboo poles.

TREATMENT

Introduction — Sojourners in the tropics as well as the indigenous inhabitants are apt to take a light view of an attack of diarrhœa or mild dysentery, but, *since at least 75 per cent of chronic ill health in the sojourner can be attributed to malaria or dysentery*—and in some places malaria is unimportant—there is every reason why their medical advisers should take great care not to fall into the same error In the present state of

him against most subsequent infections, if they are not so treated, he will eventually pass through the relapsing and chronic stages to become a permanent semi invalid with periodically recurring ulcerative colitis Further, the risk of serious development of the initially mild attack must be fully appreciated

The specific treatment of bacillary dysentery has always been singularly unsatisfactory Antitoxic serum, which was introduced about

40 years ago, is of undoubted value, and its dramatic effects in certain cases leave a great impression on the minds of those who see these, but it has never really touched the main problem of the treatment of the millions who suffer from this disease The main reasons for this are that the serum is

cases of other dysentery infections, and, finally, the vast majority of cases have to be treated under conditions where serum treatment would be difficult or impossible, and or
elaborate, and not ent
With the introdu
again raised that some of those might be of value in bacillary dysentery

Little success was achieved in this direction until recently, though a few observers are of the opinion that some of the amœbicidal drugs such as yatren and carbarsone (*vide infra*), have a specific action in bacillary infection, this view is not generally accepted The early sulphonamides gave disappointing results, though in some chronic cases they appeared to help towards the eradication of mixed secondary infections

Rather surprisingly, sulphapyridine was not used in the treatment of

doses, and its success probably depends on its reaching the large intestine in sufficient concentration

The mos ... It is given in much larg
The results s
seem to sugg
treatment of
time other d
satisfactory

Procedure —
toxæmia ulceratı
ways be kept in r

Whenever po
thing but the mil
to defæcate but
precaution may well make the difference between death and ...
though of course very frequently circumstances are such that it cannot be observed At first, practically no food should be given, but a free supply of glucose water or plain water, and later albumin water, lime whey, and chicken broth may be allowed

In the mild non toxæmic case 60 grains of sodium sulphate should be given in half a glass of water every two hours during the first 24 hours ... bsequently
alls to
nd are
ıte has
uld be
uld be
placed by the patient's bed and he should be encouraged to ... it frequently

In the more severe cases, sulphanilyl guanidine should be given This must be given in full doses, 0 10 gramme per kilogramme body-weight of

patient for the initial dose and 0·05 gramme for subsequent doses every [illegible]

lower two grammes as an initial dose and one gramme three hourly in an adult will usually be sufficient

[illegible]

remembered that opium is definitely contra indicated in cholera

Anti dysenteric serum —Shiga antitoxic serum as opposed to the so called polyvalent serum should be used for a number of reasons the Flexner organism gives rise to a serum of very low antitoxic quality Flexner infections seldom need antitoxic serum treatment and when serum is given they seem to respond as well to anti Shiga as to the polyvalent serum

The antitoxic serum that is usually available to day is concentrated and contains about 5 000 antitoxic units to the cubic centimetre An initial dose of 100,000 units may be looked upon as maximum and very often 50 000 units will be sufficient a dose of 50 000 units should be given [illegible]
rd dose if it appears to be indi
serum should be given intra
dose in normal saline In a cold
warmed to body temperature before
may follow the administration of
be tested very carefully Intra
muscular or subcutaneous injections are less satisfactory as the serum is absorbed slowly and may cause a local reaction The modern serum is treated with a proteolytic enzyme so that the danger of anaphylaxis is considerably reduced if not eliminated but in patients who have previously received any form of serum treatment and if time permits it may be advisable to precede the intravenous injections by the desensitizing course mentioned below

There is usually some reaction to the serum treatment after about 12 hours in the form of flushing of the face a slight rise of temperature and temporary exacerbation of symptoms but these rapidly pass off and general improvement is soon noted

collapse and they should be countered by injections of adrenaline and pituitrin, or (b) the later serum sickness that may come on six to ten days after the serum is administered with local pain at the site of the injection fever joint pains and urticaria A daily dose of calcium lactate will reduce the chances of both these reactions occurring

Intravenous therapy —In severe cases, whether of the choleraic type or not, this will often be indicated, and it is useful as a vehicle for the antitoxic serum Glucose added to physiological saline (25 grammes to 500 c cm , or about a pint) is the best for the ordinary severe case, but for the choleraic type of attack, hypertonic saline will probably be more

feed method

pint should

ot available

ine—may be

used with advantage

Bacteriophage —There is unanimity of scientific opinion on the fact that, *in vivo*, bacteriophage does not act as it does *in vitro*, and lyse the dysentery bacilli in the tissues The explanations of its action—if it has any action—that seems most feasible are that it converts pathogenic bacilli into non pathogenic or less pathogenic organisms, or that the lysate of those organisms that it does lyse, acts as a vaccine The writer has never been convinced from his own experience that bacteriophage has any specific action, but it is impossible to ignore the opinion of many experienced practitioners who claim that it is of definite value Some of these say that it cuts short the attack when given in doses of one ampoule (about 2 c cm) every 4 hours, others claim that it is useless in these small doses, and that *to obtain any results at all it must be given in large doses, 4 to 6 ampoules every two hours*

To summarize, world scientific opinion is still very sceptical regarding

ease, the writer however

doses, even the sceptics

universally applicable to

ies in this case

ounces of

℞ Extracti opii sicc		gr ii
belladonnæ sicc		gr ¼
Cocobutter	ad	gr 12

Vesical tenesmus and strangury will be assisted by a belladonna and alkali mixture —

℞ Potassi bicarbonatis		gr xx
Tincturæ belladonnæ		♏ xx
hyoscyami		ʒss
Infusum buchu	ad	℥ss
		4 times daily

This will also

indicated above

vented by careful

warm rectal washes

it stools can be pre

plication of lanoline,

or calamine lotion made with an oily ba e Meteorism may be an indication of severe toxæmia but in the later stages of the disease it often indicates an indiscretion in diet It may be relieved by giving charcoal biscuits or charkaolin but more active treatment with turpentine stupes, etc (*see* p 475) may be necessary Vomiting and hiccough may al o be

al o to give some form of fruit and in India and other countries where

sherbet for drinking

or other fruits as long

The feeds should be

ry two hours The diet

must be extended slowly there is a strong tradition against the use of milk in dysentery

to be excluded alt

be citrated given

or better still fort

good alternative at a later stag

very use

ful in more chronic forms of

intestinal

flora Then eggs in the for

ellies and

veg

pr

Special diets—Great success has been claime l for t e apple diet As

available

e first day followed by bismuth carbonate in do es of gr three times a day until the symptoms subside Then to prevent further recurrence the diet will have to be regulated very carefully for some time (*see* below) and ispaghula (or one of the proprietary preparations Isogel Normacol etc) a tablespoonful nightly and liquid extract of kurchi, a drachm three times a day taken for a number of weeks The be t form of

for a time, but the possibility that these absorb and retain vitamins must be remembered When some other purgative is necessary, senna pods should be used

enemata that are the mainstay of the treatment for this latter condition

Vaccines —These have never found any place in the treatment of the acute attack Their advocates have claimed useful results in chronic cases in which the original causal organisms are still present For these they advocate autogenous, or at least homologous, dysentery-group vaccines, as well as 'sensitized' vaccines, prepared by treating the vaccines with homologous serum

Others have used autogenous vaccines of various other organisms obtained from the patient's stool, on the assumption that they are the organisms causing the secondary infection of the ulcers, sometimes picking out certain special organisms, e g *Bact pseudo-carolinus*, which—for no very apparent reason—they particularly suspect The writer has seen striking results follow the administration of these vaccines in certain cases, which results he attributes to a combination of psychological effect and protein shock

If such vaccines are used with a full appreciation of their limitations —*which of course must on no account be conveyed to the patient*—they are sometimes of value in certain cases of chronic bacillary and amœbic dysentery

Vaccines prepared from cultures taken directly from the ulcer by means of the sigmoidoscope are on a slightly higher scientific plane, but have not been any more successful in the writer's experience

Diet in recurring dysentery, when acute symptoms have subsided or

Bengers food or Horlicks milk at 7 a.m, or on waking and again last thing at night

For breakfast sieved porridge with milk lightly boiled or poached eggs dry toast and butter with honey or marmite Weak tea with plenty of milk

At lunch and dinner cream soups steamed fish or chicken preferably minced or creamed but may be taken in the ordinary way if well masticated, mutton may

Orange juice, and adexolin or some other vitamin concentrates (A and D should be taken in adequate doses 2 or 3 times a day

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FLIES

THE following note on flies and methods of controlling them has been prepared from notes kindly given to me by Dr. D N. Roy, the Professor of Entomology at the School of Tropical Medicine, Calcutta

Method of spreading infection The three ways by which flies spread infection are, (i) by passing ingested pathogenic micro-organisms with their excreta, (ii) by

bottle found in the house is *Chrysomyia megacephala* and among the flesh flies

CONTROL OF FLIES

The menace of flies may be reduced in three ways, by eliminating or reducing their breeding outside the house, by killing the adults inside the house, and by screening the house, or at least the kitchen, pantry, and dining room

It is seldom possible completely to eradicate flies, but their number can usually be reduced by proper measures

houses

logical

The chemicals for treating manure are potassium permanganate, hellebore, borax and fluo-silicate

One drachm of potassium permanganate in 8 gallons of water is sufficient for 10 cubic feet of manure

Half a pound of powdered hellebore should be mixed with 10 gallons of water, and the mixture allowed to stand for 24 hours, one gallon per cubic foot of the fluid is sprayed on the manure

One pound of powdered borax for every 16 cubic feet of manure should be mixed with the manure heap by stirring Borax, when used in such small quantities, has no harmful effect on crops when the manure is later used for fertilizing purposes

One pound of sodium fluo-silicate in 15 gallons of water is applied to manure until it is fully soaked

Under this heading, pyrethrum powder might be included, but its use is not economical

times a week Shallow trench latrines used mainly at *melas* should be filled up with dry grass and leaves and burnt out or they should be covered with earth new trenches being used each day Human fæces should never be buried in trenches less than 4 feet deep

The type of latrine which completely eliminates fly breeding is the bore-hole latrine (*vide supra*)

Incinerating night-soil and street refuse has not proved as successful as was once thought The disadvantages are many it is doubtful if it can be conducted in such a way as to eliminate the breeding of *Musca* in and around the incinerator Further it is very wasteful

Screening For economic reasons the screening of the entire house is seldom possible All foodstuffs including milk should however be kept screened

he dining room should be screened

ways of destroying flies are by poison-

surface but swatting will in some

arsenic used in the form of sodium

serious accidents are likely to occur

ldehyde is one of the most commonly

container

The destruction of adult flies can be accomplished very effectively by the use of pyrethrum sprays as used for mosquitoes On walls DDT paints and sprays retain for many weeks their powers of destroying flies that settle on the treated areas

AMŒBIC DYSENTERY

Definition—A dysenteric affection that is a condition characterized by ulceration of the large intestine and the passage of numerous stools containing blood and mucus which may be acute or chronic and is caused by the protozoal parasite *Entamœba histolytica*

Discussion—There is a very strong tendency in the literature of the

a very large number of amœbæ and several of these infect man the term might imply infection by any one of a number of species of amœbæ whereas it only refers to infection by one and (iii) that whilst suggesting that the parasite attacks a number of different tissues and causes a variety of pathological changes in these which is a fact it also implies that the processes are independent whereas they are all secondary and dependent on the primary intestinal ulceration

For these reasons the writer prefers to consider the subject under the heading amœbic dysentery and to classify the secondary amœbiases' including amœbiasis *sine* dysentery as complications or sequelæ of the primary infection of the bowel wall which may have been sub clinical There are many parallel examples which the writer could quote in favour

as many that could be quoted

view as he considers that the

rescue tropical medicine from

Historical—Amœbic and bacillary dysentery were naturally not differentiated until their respective causative organisms had been identified there were however

tropics, which had been long associated in the astute minds of the early clinicians with hepatitis and liver abscess, was a different disease from the jail or asylum dysentery of temperate climates, which was never followed by these sequelæ As

species where parasitologists have be
years

The present war has again revived interest in this subject Hundreds of thousands of British and American soldiers are serving in the tropics, so that *Entamœba histolytica* is assured of vast virgin pastures and it is to be hoped that its behaviour will be carefully studied

EPIDEMIOLOGY

Geographical description —The disease has a wide distribution in all *tropical and sub-tropical countries, in the temperate zone, its position is* anomalous, for the percentage of 'carriers' (*vide infra*) is almost as high as in the tropics, but amœbic dysentery is a rare incident, and when genuine autochthonous cases occur in Great Britain, Canada or even the north U S A, the incident is usually considered a suitable subject for a special report, which is quoted and requoted in the literature for some years There are exceptions to this relativ
by residents in temperate climates e g th
1934, in the first, 1,400 cases were traced
visitors returning from this city, 75 per cent of whom had stayed in two
[illegible] 1934) and in the second during the great stockyard fire,
water
d that
which

lisease,
ommon
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fection
cillary

in origin

Seasonal incidence —As a general rule, there is no special seasonal distribution in the tropics, sporadic cases occurring all the year round *In special circumstances, for example, where flies are the main disseminators,* or when contamination of water supplies is more likely to occur at some *special season, there may be a tendency for a concentration of cases* In temperate climates it is usually a summer disease

ieavily concentrated in this age period The sexes appear to be equally
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writer
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years
ans

ÆTIOLOGY

The causal organism —*Entamœba histolytica*, a protozoan of the family Amœbidæ, is the causal organism It is a two-phase organism with an active trophozoite phase and a resistant cystic phase (*see* plate A, figures 1 to 3) There are other amœbæ which infect man, all of them are probably non-pathogenic, namely *Entamœba coli*, *Entamœba gingivalis*, *Endolimax nana*, *Dientamœba fragilis*, and *Iodamœba butschlii*

Morphology.—The **trophozoite** of *E histolytica* is an amœboid organism from 15 to 60 microns in the long axis, consisting of a clear

When the organism has been outside the body of its host for some
kind, it then becomes
lia composed of clear
The endoplasm con-
ucleus is spherical and
vesicular, containing a fine central karyosome, in unstained preparations, it is invisible, in contra-distinction to the clearly visible brighter refractile nucleus of *E coli*

The **precyst** form first becomes immobile, extrudes all food particles,

cytoplasm
T
is as f
action
where
amœba excysts, the nuclei divide and then the amœba itself divides into eight amœbulæ These remain in the fluid contents of the small intestine and pass through the ileo-cæcal valve; then, escaping from the more solid

and more static contents of the large intestine, they find their way into

by simple binary division, amœbæ find their way into the lumen of the gut, where under the sub-optimal conditions they extrude any contained food, become spherical and form a cyst wall, the nucleus divides by binary fission to produce the characteristic four-nucleated cyst, which eventually passes out with the fæces Once outside the body no further development takes place

Alternatively, the active amœbæ, during their invasion of the tissues, *may find their way into a vein, when this occurs they are carried via the* portal vein into the liver, where they cause first hepatitis, then multiple small abscesses, and eventually a large liver abscess, according to the number of the invading amœbæ and the resistance (possibly aided by therapy) of the host tissues At whatever stage this process is halted, the result, as far as the amœba is concerned, is the same, it has reached a dead end Thus, this invasion of the blood stream must be looked upon

of the ultimate design of the proto-

own species, not the destruction of

bring about Secondary invasion

reported a number of times, the

contamination of a skin abrasion

around the anus or a colostomy opening

A single individual will pass many millions of cysts in one day, the number has been estimated as from 300,000 to 45,000 000

Culture—Boeck and Drbohlav (1925) were the first workers to find a satisfact ... im generally used is a ... ion and egg albumin ... l the amœba tend to crawl up the slant

Resistance—The cysts will survive in sewage for months and for equally long in distilled water, that they will also live in chlorinated water is a fact of some considerable practical and epidemiological importance

ls, they

ngestion

disease

runs a very rapidly fatal course ... but in

e an obligatory

life cycle except

obtain nourishment and whence ... life, minute pin point ulcers

who had no symptoms of dy ... in the intestinal tract It is

containing ... have been ... cysts must at least have

therefore ... t all perso ... If the premises are correct,

such smal ... *of observed facts*

the conclu- ... inevitabl ... ry in different

regarding t ... of carr ... on the percent-

populations ... to ... cysts in their

ages of carri

stools—in different populations have been carried out for many years

placed at above 20 per cent by various competent observers Knowles and Das Gupta found *histolytica* cysts in 10 87 per cent of stools from an unselected population in Calcutta, this finding at a single examination suggests that at least double this number were actual carriers

Data are available for many countries, but no more need be quoted here, all these observations indicate that in most countries in the world there is a high percentage of carriers, a d that though on the whole the percentage is highest in the tropics and in sanitarily backward countries and communities the differences are not very great, nevertheless, except for rare incidents in temperate countries amœbic dysentery is confined to the

untries usually gives
bowel disorder, and,
o 'amœbiasis' (*vide*
slender

There is usually a higher percentage of carriers amongst convalescents, and 'contacts', *e g* soldiers returning from tropical countries where the disease has been rife

Source route and dissemination of infection —The resistant cyst is the only infective form, as the delicate trophozoite would obviously not resist the digestive juices, even if it survived long enough to be ingested A few animals have been found infected in nature—monkeys rats and dogs—and though it is possible to infect both cats or dogs in the laboratory (*vide supra*) they do not normally pass cysts and are therefore not sources of infection to others Man is thus probably the only important source of infection In patients suffering from acute amœbic dysentery, the active trophozoite forms which find their way into the intestinal lumen are swept out with the rest of the intestinal contents rapidly die and are incapa

there r

cysts

source

nor the convalescent carrier but the carrier who has never suffered from a clinical attack of dysentery However, in the opinion of the writer the epidemiological and other evidence makes it very questionable whether these symptom free carriers especially those that are encountered in temperate climates can be in any way associated with the dissemination of the disease, amœbic dysentery though the 'convalescent carrier' and the 'contact carrier' should be regarded with considerable suspicion, and should not be employed as food handlers

Invasion is always by the oral route

The media in which the infection spreads are food and water The former may become infected by means of flies—but these are not usually considered as important as they are in bacillary dysentery—by food-handlers, or by the contamination of greenstuffs with human sewage used as manure Water may be directly contaminated by human sewage, as in the historical Chicago incidents (*vide supra*) and it must be remembered that chemical disinfection, *e g* chlorination, does not kill the cysts

Immunity and susceptibility —Though there is probaly no such thing as complete natural immunity, there is evidence of varying susceptibility in different individuals, in a population exposed to infection, some escape

infection altogether, others harbour the amœbæ and pass cysts for a time without showing any symptoms, yet others suffer from mild dysenteric or diarrhœal symptoms, while, *finally, others will suffer from a serious or* fulminating dysentery

There is not much evidence of individual acquired immunity, one
on the
lly less
isitors
rs but
British
soldiers

There is some evidence of immunological response—as distinct from immunity—as complement fixation occurs when antigen prepared from cultures of *Entamœba histolytica* is brought in contact with the serum of an infected person (*vide infra*)

PATHOLOGY

The colonic lesions· Site—*The* initial ulcers are in a very large percentage of cases in the cæcum, after this the common sites are the ascending colon, the sigmoid, and the rectum The secondary ulcers are more widespread, and occur with almost equal frequency in all parts of the large intestine This is well shown in the diagram below

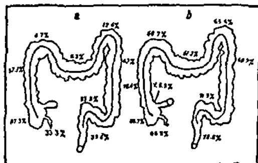


Figure 127 *Showing common sites of amœbic* ulcers (*a*) Distribution of lesions in 63 cases with only one or two ulcers (probably primary) (*b*) Distribution of lesions in 186 cases of all types (after Clark 1925)

The ileo-cæcal valve is sometimes involved, but never the ileum proper

Mechanism of production—*The amœbæ find their way* into Lieberkuhn's crypts, from there they penetrate the mucous membrane, but they do not cause much *inflammatory* reaction until they reach the submucosa, here they secrete a cytolysin which acts on the local tissues causing an outpouring of fluid into these tissues stasis and eventually thrombosis in the capillaries in these areas, and coagulation necrosis The
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whether they
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surface

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into

ment of the larger vessels, with resultant severe hæmorrhages, and possibly interference with the circulation, and gangrene of a portion of the gut, ... ll inevitably lead to perforation and peritonitis

... as follows (a) The
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er
ia,
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ous and separate, and in extreme ca... s
through the whole thickness of the gut wall (d) Finally, in the healing
...mbrane grows in from the edges and covers the base,
... or (e)

sentery
y being
ope the
gh these
comfort
to the patient ... angrene,
danger to the tissues

Another type of lesion that is usually associated with milder clinical ... carrier state is one in which there ... ulcers, which give the mucous mem ... these ulcers for some reason (not satisfactorily ... nd further Simple abrasions of the ... membrane which are believed to heal up rapidly have also been ... carrier lesion but the ... *complete* ... rotic edge, not usually undermined, with a base of granulation ... g on the muscular coat, there is a general thickening of the bowel, in which all layers take part Amœbæ are still present in the deep tissues and although most of the inflammatory processes are caused by secondarily infecting organisms *healing will not take place while the amœbæ are still there* When the amœbæ are eradicated, the ulcer either (a) heals leaving a scarred mucous ... contracture or a stricture of the bowel ... bably quite fre ... much the same conditions as does the bacillary ulcer

Secondary extra-colonic lesions—The commonest site is the liver, ... of right to left lobe infec- ... observers The ... much larger than ... to 1, the latter ... *size and direction of the two*

...d to some extent on the number ... probably to a greater extent on ... iver to this parasitic invasion—

livers already overworked or otherwise damaged being much less likely to resist such invasion—and, later, on the presence or absence of secondary infection The pathological process may go through the following four stages to reach the final one, or it may be halted at any one of them —

(a) *hepatitis*, (b) *miliary abscesses*, (c) *large 'sterile' abscess or abscesses*, (d) *secondarily infected abscess or abscesses*, or (e) *an abscess may point and burst through the skin, or into some other organ or tissue* (vide infra)

it fails, and of focal coagulation necrosis which develc ition may take place at this stage, in whi te absorption of these minute abscesses—if not, these abscesses grow and eventually coalesce producing a single large abscess of a necrotic mass of no true pus The cav are still active, and i which the amœbæ have not succeeded in 'lysing' The abscess may extend and eventually burst into some other organ or tissue, but there is evidence that the process is self-limiting evidence of secondary the abscess may be a necrotic material becor eventually calcified

On the other hand, it is not uncommon for the abscess to become secondarily infected in w beco and will perit

active abscess these can be found by scraping the cyst wall A secondarily infected abscess will consist largely of pus and liver-cell debris


Figure 128
Charcot Leyden crystals

Abscesses in other organs—Pulmonary abscess secondary to liver abscess is comparatively common, but so called primary lung abscesses have been described 'Primary' in this instance is meant to indicate 'without the intermediary liver abscess', it is not a truly primary condition

Brain and spleen abscesses are not very uncommon and are always secondary to liver abscess

Ulceration of the skin—It is doubtful if the amœbæ could ever penetrate the epidermis, but, *once* through into the deeper layers of the true skin, they are able to penetrate rapidly, to cause gangrene of large areas

of skin and to produce deep punched out ulcers The sites are practically always around the anus or a colostomy wound

The blood —There is always a sharp leucocytosis during the acute attack the count often rising to 30 000 per c mm The increase is general [illegible]

usually normo
complicated by
will usually be
macrocytic

The fæces The characteristic amœbic dysentery stool is bulky and offensive containing anchovy sauce pus much mucus and dark red blood often in clots mixed with fæcal matter at first later the stool may consist of little more than anchovy sauce pus and dark blood and in severe cases gangrenous clots which give it a very offensive smell

The reaction is acid

Microscopically the stool does not present a highly cellular picture there are many bacteria yeasts and other organisms and undigested food debris the cells that are present are mainly lymphocytes with some polymorphonuclears (both degenerated and possibly only represented by a pyknotic mass of nuclear chromatin so that their identity may be un certain) clumped red cells Charcot Leyden crystals and active amœbæ (For further details and methods of examination *see* Diagnosis)

SYMPTOMATOLOGY

Incubation period —This is usually from 7 to 14 days but it may be many months and if the onset is insidious the first serious symptoms attributable to the amœbæ may be delayed for many years when perhaps the patient h[illegible]

Clinical [illegible]
occur when t[illegible]
venience of d[illegible]
is no essential difference except in degree in the pathology of these various types —

(a) *The fulminant attack*
(b) *The typical acute attack*
(c) *The diarrhœal onset*
(d) *Chronic amœbic dysentery*
(e) *The latent infection*

[illegible]

gangrene of a loop of intestine fortunately a comparatively rare incident there may be before the final collapse a short period when local signs and

symptoms subside and stools decrease, but this is accompanied by a rapidly increasing toxæmia which any physician should recognize

(b) In the typical acute attack, the onset may be sudden with the passage of 10 to 20 stools a day ... blood, mucus a ... at first diffuse, ... then later may ... tenesmus as in ...

... thickened colon can be felt, if the abdominal wall is not too thick

(c) Perhaps the most common type of onset is the diarrhœal onset in which all the signs and symptoms noted above in the typical attack may ...

the chronic stage, the liver complications often being the first indication of the more serious nature of the condition, or a typical attack with the passage of blood or pus, or even a fulminant attack may develop from this mild beginning

(d) Chronic amœbic dysentery — For this condition the term chronic amœbiasis seems justifiable It is, as a rule, secondary to one of the acute or sub-acute types described above, but it is not uncommon to find the condition established in a patient who gives no previous history of dysentery or diarrhœa, however in such cases the infection has obviously been present, though latent, in the patient for some time The main symptoms are repeated attacks of loose stools, possibly with a little blood and mucus, alternating with periods of constipation, accompanied by slight pain and distinct tenderness in the abdomen most commonly in the area of the cæcum, descending colon, and sigmoid, the liver is tender, and a thickened bowel will often be felt distinctly through the abdominal wall There is a muddy or yellowish discoloration of the skin, and a history of loss of weight, indigestion, loss of appetite, and slight general malaise A large number of secondary symptoms ...

... is are absorbed ... often occurs without any ... of the above clinical forms ... resumed in retrospect from

last paragraph, from which the patient may be suffering, are due to this condition But the writer questions the justification of arriving at this conclusion solely on the evidence of the stool and the presence of cysts which

have the morphological appearance of *histolytica* cysts or of applying the term amœbiasis *sine* dysentery to these laboratory diagnosed cases

COMPLICATIONS

The commonest complications are hepatitis and liver abscess these will be considered separately as though they are ætiologically linked with amœbic dysentery they constitute a separate syndrome Other complications are —

Hæmorrhages —The deep sloughing that occurs in the bowel wall often

of the bowel wall at the site of a deep ulcer this is an uncommon accident and seldom occurs except in the case of gangrene of a segment of the colon which subsequently ruptures

operation Retro colonic abscesses also may occur as the results of a leak from or the frank perforation of an amœbic ulcer retro peritoneally The signs and symptoms will be very similar to those of an appendix abscess and will often be in the locality of the cæcum to make the picture more

omy
g of
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the
muscle layer very painful on pressure and exuding a purulent discharge The ulceration is liable to spread with alarming rapidity unless controlled by emetine injections

Rogers
upon as sec
quency witl
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more recent
dietetic in origin a sequel to restriction or to mal absorption of essential food elements particularly protein

DIAGNOSIS

The clinical dysenteric attack will have to be differentiated from dysentery from other causes (*see* p 368)

It is of primary importance that this differentiation should be made in order to ensure the correct treatment (there being radical differences in the treatment for bacillary amœbic and other dysenteric conditions) but it is also important from the point of view of prognosis especially to provide an indication of the complications that are to be expected

Points of differentiation between bacillary and amœbic dysentery are given in table VIII (p 413)

Laboratory diagnosis · Stool examination —The first point to be borne in mind is that the examination must be made on a fresh stool Amœbic trophozoites will not be found unless the specimen is absolutely fresh, even cysts begin to degenerate in an hour or so in some stools In a cold country, it will be necessary to keep the specimen warm, both before and while it is examined, if the activity of the amœbæ is to be maintained, and it is important for proper identification that they should be active If possible e g in chronic cases, the patient should always go to the pathologist and pass a fresh stool for him to examine, rather than send the specimen to the pathologist If a stool cannot be passed to order, it is a good practice to insert a rubber catheter into the rectum, *rotate it so that the end moves* about, and from the 'eye' of the catheter it will usually be possible to obtain a small sample suitable for examination

The stool must be inspected carefully and its **macroscopical** characteristics noted (see p 433)

The reaction of the stool should be tested with litmus paper, it will be acid in amœbic dysentery

For **microscopical** examination, two preparations must be made—(*a*) in saline and (*b*) in iodine

(*a*) *In saline* A small portion of stool if possible a piece containing blood or mucus is picked out on a platinum loop and transferred to a watch glass containing a few drops of normal (0.85 per cent) saline, a fine emulsion is made any mucus present being teased (the emulsion should be such that small print can be read through it), a ring of vaseline is arranged on a clean slide, a drop of emulsion is placed in the centre, and a thin coverslip is placed over it The slide is placed on the microscope stage—which should be warmed if necessary—and examined with a 1/6th objective

(*b*) *In iodine-eosin* A 5-per-cent potassium iodide solution is saturated with iodine, an equal amount of saturated solution of eosin in normal saline is added immediately before use A portion of stool is added and a slide prepared as with saline There is some advantage in examining the saline and iodine-eosin specimens under the same coverslip

[illegible] re is a definite advantage in employing the [illegible] nique (see p 620) in examining stools for [illegible] a loopful of material is taken from the

The saline preparation must be examined immediately, and if there is any delay it must be kept in the 37°C incubator, the iodine-eosin specimen may be kept for some hours

If the examination is to be thorough, several 'smears' of each kind must be made with samples taken from different parts of the stool

The general microscopical nature of the stool should be noted, and amœbæ should be looked for and, if found, identified There should be little doubt about the identity of an active trophozoite of *E histolytica* [illegible] could only be confused with *Entamœba* [illegible] nœbæ, but a sluggish or dead amœba is [illegible] ch may show some amœboid movement [illegible] iost acute stages are more readily found than the trophozoites, also have to be differentiated from other amœbic and flagellate cysts, and from *Blastocystis hominis* About the identity of a single four-nucleated cyst in the saline or in the iodine preparation there will often be doubt, but, when several specimens are found in each, the doubt will usually be removed, of course, frequently both *E histolytica* and *E coli* are present

When trophozoites are present, there are usually few cysts and *vice versa*

The finding of active *E histolytica* with contained red cells, or of undoubted precysts, is diagnostic of amœbic dysentery The presence of

cysts is also said to be diagnostic of some ulceration, but this may be of the pin-point or somewhat questionable shallow type

Culture of the fæces for entamœbæ is a laboratory refinement that is certainly worth undertaking if a well-equipped laboratory is available

In a convalescent at least six consecutive daily examinations should be carried out—and found 'negative'—before a patient can be proclaimed as free from infection

TABLE IX

Important morphological characters of E histolytica *and* E coli

	Trophozoite stage unstained E histolytica	*E coli*
Size when rounded	10–30μ	20–30μ
Movements	Very active in fresh Later finger like clear podia thrust out fro mob le body	- pseudopodia
Colour and appearance	Glassy clear greenish or yellowish	Ground-glass
Inclusions	Red cells usually no bacteria	No red cells* bacteria yeasts, starch granules and even other protozoal organisms
Nucleus	Usually not seen	Usually visible
	Encysted stage unstained	
Size	6–20μ.	10–33μ
Shape	Spherical	Spherical
Cyst wall	Thin	Thicker
Colour and appearance	Clear greenish or yellowish	Like ground-glass
Chromatoid bodies	Usually bars with smooth rounded ends present in most cysts	Filamentous or splinter like, seen only in about 5 per cent of the cysts
Glycogen mass	Often very prominent especially at binucleolar stage	Sometimes well marked in early stage but soon disappears
Nuclei	Usually invisible	Visible
	Encysted stage iodine preparation	
Cytoplasm	Greenish yellow smooth and hyaline	Yellowish brown granular
Chromatoid bodies	Indistinct	Not visible
Nuclei	1 to 4 (rarely 8) minute central karyosome	1 to 8 (rarely 16 or more), karyosome large and eccentric
Glycogen mass	Yellowish-brown diffuse	Dark brown diffuse with indistinct outline

* Some strains of *E coli* have been known to ingest red cells in culture if these are introduced into the medium

The only other finding to which ... presence of Charcot-Leyden c... that there is a high degree of ... in stools, but they are not diagnostic

Complement fixation test—It is claimed that a 90-per-cent correct diagnosis can be made by means of complement fixation technique with an *E histolytica* culture extract as the antigen The results obtained by this test are not entirely consistent, and its specificity is not accepted by all workers

Other methods—S... appearance of ... specimen may ... examination w... the whole, *x*-rays are not very helpful in an acute or sub acute dysenteric attack

TREATMENT

Historical—Ipecacuanha has been used in the treatment of dysentery for centuries, it was certainly used in India in 1660 But at this time it was usually given in small doses in 1846 Parkes revived the interest in this drug and gave it in large doses In 1866 Macnamara gave the alkaloid emetine that had been isolated from ipecacuanha by Pelletier in 1817, by mouth and from the year 1886 ipecacuanha was given regularly in hepatitis The emetic properties of emetine were recognized and ipecacuanha *sine* emetine had a short vogue (Neubert 1913), but in 1912 Vedder showed that it was the emetine that killed the amœbæ and that the efficacy of ipecacuanha depended on its emetine content

In 1912 Rogers demonstrated that emetine could be injected subcutaneously and that it acted as a specific in amœbic dysentery and amœbic hepatitis He standardized the treatment with this valuable drug that has made such a vast difference to the expectation of life of the white soldier in the tropics

Later work by Dobell and others cast doubt on the specific action of emetine on amœbæ *in vivo* and the present opinion is that its action is indirect

Emetine bismuth iodide (EBI) an emetine compound which it was possible to administer without causing vomiting was introduced with the idea that a more direct action on the amœbæ in the bowel could be obtained by the oral administration of the drug

Holarrhena anti-dysenterica (or *kurchi* bark) is an ancient Indian remedy for dysentery Chopra and others have shown that an extract of this bark has a specific action in amœbic dysentery though distinctly less than that of emetine

Many synthetic drugs have been introduced during the last twenty years *e g* arsenical preparations such as stovarsol and carbarsone (Reed *et al* 1932) iodine compounds such as yatren (Mühlens and Menk 1921) and acridine compounds such as rivanol for all of which a specific action on the amœba is claimed

Treatment of the acute attack—Emetine, one of the most useful and almost certainly the most ...

abled, and yet others probably killed, by a course of 12 grains in 12 days (*vide infra*) That is to say, as in the case of most drugs, the personal factor is important and it is essential to play for safety

Directly a diagnosis of amœbic dysentery has been made, a course of emetine should be started without delay To an adult, six injections of one grain each should be given during the first six days, after which an interval of three to six days should be allowed and the course repeated, in very mild attacks that respond immediately, three injections in the second course will be sufficient After this, an interval of at least two weeks should be allowed before any more emetine is given, whatever the circumstances, few cases in which the infection is confined to the bowel will require any further emetine, but the more serious hepatic infections will

For small women and children, the size of the individual dose of emetine should be reduced proportionately

Routine —An ounce of castor oil with 15 minims of tincture of opium should be given on the first day followed by one grain of emetine hydrochloride given intramuscularly *the patient should be confined strictly to bed* and given a light fluid diet mainly consisting of low fat content milk or milk preparations From the following day or from the evening of the same day, if the castor oil was given early he should be given 2 drachms of bismuth carbonate in a glass of water four-hourly night and day and one grain of emetine intramuscularly 2½ hours after the first daily dose of bismuth The bismuth may be reduced to thrice daily if the main symptoms—pain and frequent stools—subside and discontinued altogether in these circumstances when the first course of emetine is complete other

is being taken a do e of salts should be given to ensure comp ete evacuation of the drug as otherwise its action is likely to be cumulative Or for this immediate follow up course emetine bismuth iodide (EBI) is favoured by some workers This is given in 3 grain doses for a week to ten days in hard gelatin capsules or as salol-coated pills taken at night two hours after

ecessary by some sedative mixture opium 15 minims These precau

can be rounded off by prescribing

of the sigmoidoscope

The vast majority of cases will respond to this course of treatment Those who do not must be looked upon as chronic cases and treated accordingly (*vide infra*)

Diet —As stated above at first the diet must be light and fluid lime

nger s food fruit
light solids milk
food with much
semi vegetarian

dietary which does not contain too much roughage should be maintained for some time, as this tends to keep the large bowel content alkaline

Toxic effects of emetine —T
the ill advised admini tration o
and serious on account of the
who are being po soned Durin
of inexperienced medical officer
da ly for long periods and litera
often quite unaware on account of the frequent evacuations from hospital that are inevitable in war time In the subsequent years he has seen athletic young men s hearts disorganized for years through the failure of their medical advisers to realize that they should advocate strict rest in bed during the whole time a

hich it prod ices
m with a fall of
bl result of any
und ie effort It also may cause acute mental depression neuritis myositis

changes in the skin and nails, and diarrhœa, which last named is likely to be attributed to the dysenteric condition

Other
rest at night
or so until th
aided by hot ... ons of turpentine stupes

Tenesmus is less common but can be relieved in the same way as in bacillary dysentery (*vide supra*)

Treatment of chronic amœbic dysentery —This presents one of the major problems of tropical medicine The action of emetine is specific if given early, and every effort should be made to give an efficient course in good time However, in the chronic stages, the action of emetine is very disappointing, and in the absence of hepatitis, it is questionable if it should be employed at all

At this stage, drugs that have a direct action on the intestinal mucosa appear to act better than emetine, and therefore emetine bismuth iodide, given as indicated above, is of value However, in the writer's experience, carbarsone is the most useful drug at this stage, provided that there is no hepatitis or cirrhosis, other drugs, su
chiniofon, diodoquin, vioform and ri
their special advocates, and it may
obstinate case, but even then a cur
bowel washes are also given

Chiniofon (yatren)
(about 4 grains)
increased to two p
if it can be tolerated, for ten days

Vioform, also best given in the form of keratin-coated capsules and diodoquin are given in doses of 0 63 gramme three or four times a day In the case of the former, it is best to limit the course to 10 days, as toxic effects have been reported, but the latter can be continued safely up to a full three weeks

For medicated bowel washes, chiniofon (20 c cm of a 2 5 per cent solution) is the most popular, and considerable success has been claimed with it by some workers, although the writer has been less fortunate Manson Bahr (1939) uses a combination of EBI by mouth and chiniofon per rectum, which he claims is almost infallible

Other bowel medicaments have been used with success, *e g* rivanol which is recommended in a strength of 1 in 2 000, but the writer has usually found that silver nitrate solution combined with the administration by mouth of some 'specific' drug, *e g* carbarsone, is as good as the far more expensive yatren

All medicated bowel washes must be preceded by a 2 per cent sodium bicarbonate enema, which the patient retains for about 10 minutes and then passes as completely as possible After this, the medicated retention-enema is run in slowly—about 8 ounces is usually sufficient for the patient to retain comfortably, he should retain this as long as possible, up to 8 hours in the case of yatren (2 5 per cent) Silver nitrate is given in increasing strength, from 1 in 750 up to 1 in 250 or even stronger If the enema causes much pain, it can be washed out immediately with normal saline, but if not, it should be retained as long as possible, up to about 5 hours The patient should lie on his left side whilst the wash is being run in, and should then assume the knee elbow position to allow it to run well up into the transverse colon and, one hopes, beyond

It is usually necessary to keep up the bowel washes for at least a fortnight before much benefit will be apparent, except some soothing effect

which is often an almost immediate result and they may have to be continued daily for a month or more Later, as improvement is established, the washes may be reduced to one every other day

After this course, extract of kurchi and ispaghula (*vide supra*) should be prescribed for at least two months

Vaccines—In chronic ulcers, which are mainly maintained by secondary infection, but in which the amœbæ are still active, a vaccine, preferably made from an organism obtained directly from the ulcer by means of the sigmoidoscope, is sometimes helpful (*see* p 412) When the secondary bacterial infection is overcome, the tissues are apparently better able to deal with the amœbic infection

Diet—Great care must be exercised in advising patients about their

As secondary infection of the ulcers is an important factor at this stage, it may be useful to attempt to influence the intestinal flora by giving bulgaricized milk (in India the ordinary *dahi* will serve the same purpose), with or without the addition of lactose, a heaped tablespoonful first thing in the morning

PREVENTION

Man is apparently the sole source of infection so that proper fæcal disposal and sewage treatment are the most important measures It should be remembered that the cysts—the infective form—will survive in a septic tank for some months

Water is not usually incriminated—although it was the vehicle in at least two historic epidemics, however, it cannot be ignored as ordinary chemical methods of water sterilization will not destroy cysts although almost any form of filtration will The writer believes that more attention

value as a preventive measure, as such persons pass few cysts, it is important however that, when they become convalescent, they should be followed, examined periodically, and, if they are found to be passing cysts treated

Most of the measures for prevention are thus general sanitary measures, and the only special preventive measure is with reference to carriers (*quod vide*) In institutions and households a systematic stool examination should be carried out amongst all food handlers and the 'carriers' weeded out and treated What is at present impeding legislation in the matter of enforcing such precautions in public eating places is the uncertainty regarding the importance of the 'cyst passer' in temperate

countries, but the measure should be rigidly enforced in the case of the convalescent carrier, especially in tropical countries

PROGNOSIS

This will depend on how soon treatment is undertaken and on its efficacy It is impossible to give figures, but an initial attack is very rarely fulminant Almost all the deaths that occur as a direct or indirect result of amœbic dysentery are due to neglect of treatment in the early stages There is however a small percentage of cases in which the symptoms persist for months and even years, despite (ordinarily) efficient measures

With the establishment of hepatic complications the prognosis becomes graver (*vide infra*)

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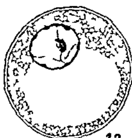
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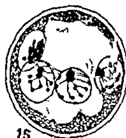
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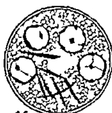
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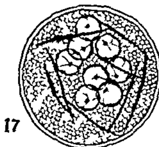
PLATE XII (Cysts)

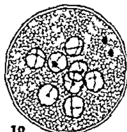




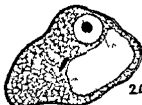










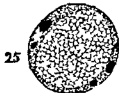












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The Iron-hæmatoxylin Staining Method*

The accurate differentiation of *Entamœba histolytica* from other amœbæ and cysts requires experience In most cases an identification can

anyone who wishes to learn to identify amœbæ to use the iron hæmatoxylin

mission

ing by
rocess
ly and

Leave

in 3 minutes

3 Transfer to 70% alcohol for 2 minutes
4 Transfer to 70% iodine alcohol for 2 minutes This is prepared by adding sufficient tincture of iodine to the alcohol to give a dark amber color

1

1
1

13
14

15 Place in xylol for 2 minutes
16 Mount in balsam or gum damar using a No 1 cover glass In place of step 14 two changes of dioxane may be used for dehydration[3]

---

* [1] *Schaudinn's Fixing Fluid* Distilled water saturated with mercuric chloride 2 parts 95% alcohol 1 part. Add 5 to 10 cc of glacial acetic acid to every 100 cc of this mixture

[2] *Iron Alum* 2% aqueous solution of ammonium ferric sulfate

[3] *Hematoxylin Stain* 0.5% aqueous solution of alcoholic ripened stain Stain solution is prepared by dissolving one part of hematoxylin crystals in 10 parts of absolute alcohol This may be ripened in one of several ways

1 By the ordinary slow process of standing for several months
2 By placing in an incubator for two weeks
3 By adding hydrogen peroxide
4 By adding carbolic acid and then boiling

The ripened stain should be diluted to 0.5% by adding distilled water If upon using the stain is found to be insufficiently ripened a few drops of hydrogen peroxide or of carbolic acid should be added to each 100 cc of solution and the solution heated

periods of reactivation and advance At this stage also, emetine will often control the condition, but it must be given for a longer time

The stage of liver abscess will usually present a more definite clinical picture, but nevertheless there are many cases that show few or none of the classical signs and symptoms, and cases are on record in which an abscess has suddenly burst, *e g* into the lung, without any previous record of ill health

The patient may give a history of previous illness that would corres

have a grey look with a sub-icteric tinting of the skin and sclerotics, but

of fever develop nt occa- ugh con- ng His plain of dysphagia indigestion severe liver pain, which is usually stabbing in nature and very often referred to the right shoulder, and an irritable cough The leucocyte count will be 20,000 per c mm or more but this is not a constant finding (*see* figure 130), and a normal or a lower

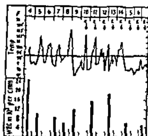


Figure 130 Shows the inconstancy of the leucocytosis in liver abscess the condition responded to emetine treatment

be caused when the thorax over the liver area is pressed between the hands, there will also be tenderness in the intercostal spaces, and there may be some inter costal œdema

Other physical signs will depend on the size and position of the abscess If it is in the left lobe or in the palpable portion of the liver below the costal arch, it may produce a local bulge in the abdominal wall which it is possible to recognize as an abscess, it may be tense, but it is more usually soft and can ir from a hydatid cyst by the absence of

There will often b se of the right lung

The abscess may point and eventually rupture externally, laterally through the chest wall, or below the costal margin, or it may

referable to the lung or p

ruptures into the lung, the contents are immediately coughed out, and the patient may die of dyspnœa, or of shock, but, if he recovers from the immediate effects, complete recovery is very common The walls of the abscess collapse and close the opening and sepsis may be obviated

Plate XIII

Amœbic liver abscess

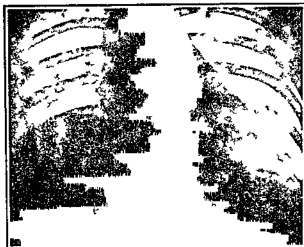


Fig 1.—Showing the high raised right dome of the diaphragm it has an unusually clean cut outline The heart is pushed over to the left Two pints of pus were obtained by aspiration

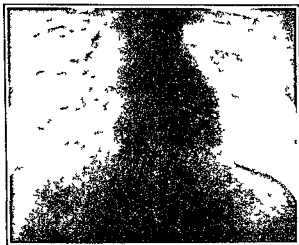


Fig 2—Showing a local dome-shaped swelling superimposed on the right dome

PLATE XIV

Amœbic liver abscess

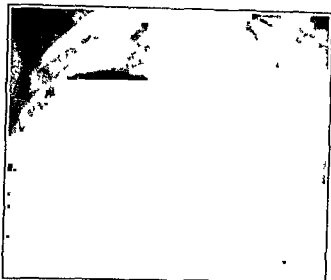


Fig 3—Showing another high right dome

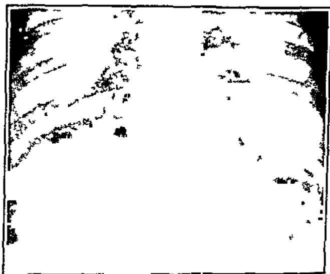


Fig 4—In this case the diaphragm is scarcely raised but the lung is apparently involved Two days before this was taken the patient coughed up over a pint of pus he made an uninterrupted recovery

Rupture into the pleural cavity is far less common Other common directions are into one of the hollow viscera stomach, duodenum or large intestine Rupture into the pericardium, the gall bladder the pelvis of the kidney or into the loose perinephric tissue, and into the peritoneal cavity has been reported (*see* figure 131)

Diagnosis — If the patient gives a history of living in the tropics under conditions in which he is likely to have acquired an amœbic infection not too much attention should be paid to whether he has actually suffered from amœbic

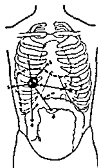


Figure 131 Diagram showing some of the directions in which a liver abscess may burst

1 Into the lung or pleural cavity
2 Into the stomach
3 Into the duodenum
4 Into the cæcum
5 Through the skin
6 Into the pericardium

the therapeutic test with emetine is of value in the early stage of simple hepatitis, a definite response will usually follow three daily injections, if it is suspected that the stage of miliary abscesses has been reached at least six should be given and even when there is a large abscess, some distinct clinical improvement will usually follow six injections but it may be advisable to persist up to nine The **blood picture** will give additional evidence but it must be remembered that the leucocytosis is neither as constant nor as high as one might expect The final court in the diagnosis of liver abscess is an **exploratory puncture**

Technique of exploratory puncture —A large serum syringe with a needle of moderate bore (about no 9) not less than 3½ inches long is used A local anæsthetic should be injected at the point selected The needle is inserted either at a point where the abscess appears to be pointing or when there is no such indication in the 8th interspace in the mid axillary line and thrust into the liver substance at first in a slightly upward and forward direction towards the right cupola of the diaphragm if no pus is obtained the needle is partly withdrawn and pushed in again in another direction a third or even a fourth attempt may be made but if these fail it must be assumed that there is no large abscess present If the anatomy of the liver is visualized if common sense is used and if care is taken to avoid the gall bladder and not to thrust the needle in to a depth greater than 3½ inches in any direction the

aspirated *vide infra*)

Differential diagnosis —In view of the very considerable variability in the signs and symptoms of amœbic hepatitis and liver abscess, and the possible absence of any especially in the early stages, an adequate discussion on this subject would cover half the field of internal medicine In

these circumstances, it will be best to give a short classification, with a few examples, of the diseases that *may simulate*, or be simulated by, amœbic hepatitis and liver abscess

Febrile conditions **Long fevers**—Typhoid, tuberculous, and *Bacillus coli* infections, the Pel-Ebstein syndrome, undulant fever, and kala azar

Short *fevers*—*Malaria*, relapsing fever, rat-bite fever, and leptospirosis

In most of these conditions either rigors or profuse sweating will sometimes if not usually, occur, and either of these symptoms will *heighten the similarity*

[illegible] stion, active or cirrhosis, syph- [illegible]), gumma, carcinoma, and pyæmic abscesses

Extra hepatic conditions—Pneumonia, basal pleurisy and empyema, cholecystitis and suppurative cholangitis, *pyelonephritis*, *perinephric* abscess, and sub-phrenic abscess, appendicitis with complications

TREATMENT

General—The patient must be confined to bed whenever a definite [illegible] He should be given [illegible] ng the febrile bouts,

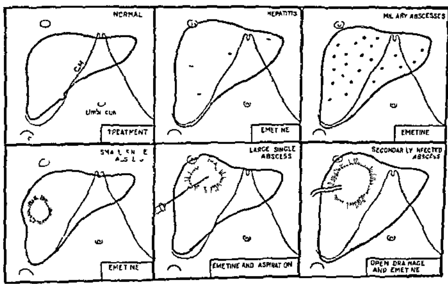


Figure 132 Showing five stages of liver involvement and the treatment of choice in each case

[illegible] local applications, hot fomentation or anti- [illegible] le and aspirin phenobarbi- [illegible] with magnesium sulphate, liquorice powder, or a mercury and aloes pill (*see* p 51)

In severe cases, a daily dose of intravenous glucose will be beneficial

Specific—It is in the hepatic complications of amœbic dysentery that emetine is of the greatest value, and, in amœbic liver abscess, the combined

treatment of emetine administration with aspiration is a very great advance on the previous method of open operation in which the death rate was always above 40 per cent

At every stage of the invasion of the liver by amœbæ, emetine is of value Some indication has already been given of what may be expected from emetine administration

While in the earliest stage of hepatitis, three one-grain injections will

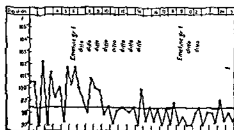


Figure 133 Showing a rapid response to emetine, the process had probably reached only the miliary-abscess stage

Aspiration — Even when a large abscess has obviously formed, it is quite often possible to control the condition by emetine alone without aspiration However, if the evidence points to a large abscess, or if preliminary treatment, while perhaps controlling the fever to some extent, has obviously not completely halted the pathological process, it will be as well not to postpone aspiration any longer If emetine has not already been given and if the urgency of the occasion seems to permit, it should be given before the operation, if not, then after operation, until the fever is controlled or 12 injections have been given In a serious condition like this certain risks (*see* p 439), which might be unjustifiable in other circumstances, have to be taken with emetine dosage (*e g* cases of figures 134 and 135)

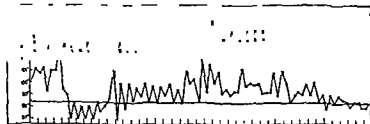


Figure 134 Showing delayed response to an 'overdose' of emetine (*see* text)

In the case of which the temperature chart is shown (figure 134), aspiration was seriously contemplated as his temperature had not fallen after 12 emetine injections, but instead emetine was given again, and aspiration obviated In another case (figure 135) both aspiration and emetine were necessary, but the

After the abscess has been aspirated, if the fever continues, it may be advisable to give further emetine injections The risk of giving these may have to be weighed against the risk of allowing the pathological process in the liver to extend Eventually, even in an uninfected abscess, the time may come when open drainage will have to be considered, but this should be postponed as long as possible, for once a drainage tube is put in, contamination is inevitable

open drainage
if the surgeon,
be mentioned

Figure 135 This was a very bad case two liver and one pleural aspirations were required as well as 20 grains of emetine

Prevention —*Basically the prevention of liver abscess is the prevention of amœbic infection* There appears to be no danger of liver abscess developing in the intestinal amœbic infections that occur in temperate climates, but in a tropical country *such an infection must be looked upon as a potential danger,* and certainly in all cases in which there is frank

Emetine appears
(*vide supra*)
the consump-
ial amœbiasis,
re, and has no

ss is poor, the
ometimes reported as
70 per cent—in pre-emetine days

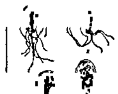
In amœbic hepatitis, by efficient treatment, it should be possible to prevent abscess formation *in every case,* but later, when an abscess has *developed,* the death rate is still from 10 to 15 per cent

OTHER PROTOZOAL AND METAZOAL DYSENTERIES AND DIARRHŒAS

FLAGELLATE DIARRHŒAS GIARDIASIS

Discussion —The commonest intestinal flagellates are *Trichomonas intestinalis* and *Chilomastix mesnili* which infest the cæcum and large intestine and *Giardia enterica* (*Giardia intestinalis* or *lamblia*) which is

this does not mean that the flagellates cause this condition on the contrary the condition of the bowel probably encourages the flagellates to



which he does not believe exists he will make no further reference to the other flagellates and will discuss only giardiasis

Historical —Leeuwenhoek discovered the parasite whilst using his primitive microscope in 1681 It was rediscovered as a human parasite by Lambl in 1859 and given the name *Lamblia intestinalis* but as another species of the genus had previously been described and given the generic name *Giardia* Lambl s parasite

was renamed *Giardia intestinalis* It was later pointed out that the specific name *intestinalis* was already occupied and that *the correct name is Giardia enterica* The name *Giardia lamblia* is also used, but is not in accordance with the rules of nomenclature

Epidemiology —Giardiasis occurs in all countries, but is probably more common in the tropics It is found in persons of all ages, but it produces more definite symptoms in children than in adults It was found in 6 27 per cent of about 20,000 stool samples from a mixed population *examined in Calcutta between 1935 and 1938* In children, the general infection rate is higher

There appears to be no reason for attributing any racial predilection to this infection, and, although the incidence is to some extent inversely [illegible] not uncommon

[illegible]

the highest infection rate have acquired any tolerance to the ill-effects of the infection, the writer has frequently seen symptomatic giardiasis in such persons

Ætiology and pathology —*Giardia enterica* is a flagellate parasite with a trophozoite and a cystic stage The former is pear-shaped and dorsally convex, it has a 'sucking disc' in its ventral concavity, and four pairs of flagella, it has a colourless granular cytoplasm, and two nuclei (not *seen in the unstained specimen), in size it varies from 10 to 20μ in length* and from 5 to 15μ in breadth, it is actively motile in the freshly passed fluid stool, but soon loses its flagella and motility in a formed or stale stool The cysts are oval, 8 to 12μ in length and 7 to 10μ in breadth, they are colourless, and have four nuclei and a well defined cyst wall

The parasite lives and multiplies in the intestinal tract, from the duodenum to the cæcum Both the cysts and the trophozoites are found in [illegible] will be found in larger numbers in samples

[illegible] ched to the intestinal mucosa which they [illegible] excess of mucus It is also very probable that they affect the function of the mucous membrane and interfere with [illegible] to giardia infestation, [illegible] responsible for [illegible] erties [illegible]

treatment, and one is naturally [illegible] to giardiasis However, it is quite obvious that there are many persons with giardia infection, who suffer no recognizable ill effects

The most constant symptoms are (*a*) diarrhœa—the stools are usually loose and watery, but may be definitely *fatty*, (*b*) abdominal pain [illegible] with flatulence or discomfort, either [illegible] loss of appetite, and sometimes with [illegible] by defæcation, or in the *lower segm*[illegible] and (*c*) irregular fever

Children also are usually irritable and tiresome, and develop capri[illegible] recognized as being [illegible] have shown [illegible] sore tongue, [illegible] of total fat [illegible] nce of all the

In addition, adult patients often feel definitely ill and weak, and they may exhibit nervous symptoms, such as irritability and anxiety

Abdominal tenderness is constant in the cases with symptoms, this is usually in the epigastrium, but sometimes in the region of the cæcum

Treatment —Of the innumerable treatments advocated none proved really successful until Brumpt (1937) and Martin (1937) introduced mepacrine (atebrin), which appears to be a specific

A large percentage of complete cures will be achieved with a course of 0 1 gramme three times a day for five days Children should be given smaller doses (*see* p 101) A second course after an interval of about a week will be necessary in a few cases If there is any doubt about the cure it is advisable to give this second course

CILIATE DYSENTERY BALANTIDIASIS

Although balantidiasis is a rare infection there seems no possible question that it occurs and may be serious Some 250 cases have been recorded

universal
countries
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common
od Two

ave been reported from North America, and several from South America and Africa

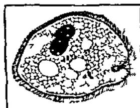


Figure 137 *Balantidium coli*

Occupational incidence —It occurs in swine-herds and pork-butchers and other persons closely associated with pigs

Ætiology —*Balantidium coli* is a ciliate protozoa a natural parasite of pigs, to which it appears to do little harm It is transmitted to man apparently by food contamination Experimentally it is transmitted with great difficulty

Pathology —The parasites invade the mucosa of the large intestine apparently in exactly the same way as does *Entamœba histolytica* The ileum has also been involved Entering the crypts of Lieberkuhn, the parasites secrete a kind of cytolysin, and penetrate into the submucosa, and thence even into the intestinal lymph nodes The ulceration produced is similar to that of amœbic dysentery Perforation has been reported

Symptomatology —This is again indistinguishable from that of amœbic dysentery The onset is often very insidious but the condition may develop seriously, and it is usually very persistent Anæmia is a marked feature and later cachexia develops

Diagnosis will be made only by finding the *Balantidium coli* in the stool It is a large parasite easily seen with the low-power lens

Treatment —This has not been very satisfactory Large (dangerous) doses of emetine, gr 1 daily for 15 to 20 days, have produced a cure in a number of cases, and recently methylene blue—administered by mouth in

2-grain pills and as an enema in a strength of 1 in 3,000—has been used with some success Drachm doses of carbon tetrachloride have also been used successfully

Prognosis —A number of deaths have been reported The mortality can be placed at between 10 and 20 per cent

In some cases, the infection has persisted for from four to fifteen years

COCCIDIOSIS

Infections with the coccidium, *Isospora hominis*, are not rare in the tropics and sub-tropics, and are usually associated with sub-acute dysenteric symptoms

Epidemiology —The infection has been reported in most countries in the tropics and sub-tropics, but rarely in the temperate zones The apparently greater frequency in the Mediterranean area probably reflects only the fact that greater attention has been paid to it there In routine stool examinations in India, it is not such a rare finding that observers think it necessary to report each case nine cases have been encountered in the last twenty years at the Calcutta School of Tropical Medicine (Das Gupta 1934)

The majority of the infections reported have apparently been in adults

Ætiology and pathology —The parasite, *Isospora hominis*, infests the small intestine and invades the mucosa The oocysts, which are found

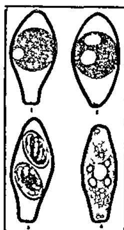


Figure 138 *Isospora hominis*

(Dobell and O Connor 1921)

1 Oocyst with unsegmented protoplasm, as usually passed in stools
2 Later stage, nucleus divided into two
3 Fully developed oocyst containing two spores—each containing four sporozoites
4 Degenerate oocysts which have failed to develop

Infection of man takes place in the oöcyst stage by the oral route

Symptomatology —Symptomless infections are not uncommon Infection is usually associated with mild chronic diarrhœal symptoms, some malaise and mental depression loss of appetite and weight, and occasionally epigastric discomfort

The stools are light-coloured, contain much undigested food, and show a tendency to be fatty

Diagnosis can be made only by finding the oocysts in the stools The only other characteristic finding, which is almost constant, is Charcot-Leyden crystals

Treatment —No entirely satisfactory ... not usually very persistent ... l of a ... the most successful procedures ... are those of ... he important

the ge

syndrome caused by these parasites is discussed Diarrhœal symptoms have been associated with two other trematodes, *Fasciolopsis buski* and *Heterophyes heterophyes*, and two nematodes, *Œsophagostomum apiostomum*

a catarrhal condition of the gut which leads to diarrhœa, pain in the abdomen, œdema and ascites, and a serious condition of ill-health, which develops gradually

Most antihelminthic drugs will effect a cure, *e g* carbon tetrachloride or tetrachlorethylene given in doses of 3 or 4 c cm with the usual precautions

Heterophyes heterophyes infests dogs, cats and other carnivores and man They similarly develop in snails, the cercariæ are ingested by fish, and man becomes infected by eating insufficiently cooked fish

If present in the small intestine in large number, they also produce a catarrhal condition of the mucous membrane The clinical picture is similar to that associated with *Fasciolopsis* infection

In the treatment of this infection, most of the ordinary anthelmintics have been tried, usually with good effect

Nematode diarrhœas and dysenteries —*Œsophagostomum apiostomum* is a common nematode in monkeys in West Africa, and it occurs also in Asia, it has not been reported in India The larvæ are swallowed, and reach the cæcum where they bury themselves in the mucous membrane, and develop The nodule thus formed bursts into the lumen of the cæcum, and the worm attaches itself to the mucous membrane Secondary infection

worms themselves

ms may be either

nt treatment, but

probably other anthelmintics would prove as satisfactory

Strongyloides stercoralis, to which further reference will be made, also causes a diarrhœa

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CHRONIC POST-DYSENTERIC ULCERATIVE COLITIS

Discussion —Ulcerative colitis is not an exclusively tropical condition, and in fact has received far more attention in cosmopolitan medical literature than in that section of medical literature that deals mainly with tropical diseases There has been much inconclusive discussion on the ætiology of so called idiopathic ulcerative colitis we are little concerned with this for whether or not bacillary dysentery is a common cause of the ulcerative colitis of temperate countries certainly a chronic ulcerative colitis is not an uncommon sequel to both bacillary and amœbic dysentery in the mœbic exists t least

Ætiology —As has been indicated above the condition we are considering here is not *now* maintained by either *Entamœba histolytica* or one of the recognized dysentery bacilli and the finding of a small number of organisms of either of these genera in the stools does not necessarily indicate that the main pathological process is maintained by them For ... small

independent of a chronic ulcerative condition of the bowel Similarly a 'carrier type of amœbic infection may exist in one part of the gut when elsewhere there is a non specific ulceration

The principal micro organism that is now maintaining the pathological process will probably vary from case to case Streptococci are usually recovered most readily from the ulcers but there is still much work to be done on the identification and classification of the flora of these ulcers

Cultures from the stools may be misleading and the true culprit is likely to be identified only by taking swabs directly from the ulcers after colonic lavage with the aid of the sigmoidoscope Bargen s diplococcus which it is claimed is frequently present in the ' idiopathic form has seldom been identified in the tropics

The main predisposing factor is of course the damage done to the gut mucous membrane and deeper structures during the primary (specific) ulceration It is not difficult to understand how such large denuded areas fail to heal whilst in more or less continuous contact with the septic gut contents However as we know that healing does frequently occur we m st a ng dow wh d d

even in the well to do patient from long periods of restricted diet

PATHOLOGY

The ulcers may be in any part of the colon but are usually in the sigmoid or rectum The cæcum is the next most common site The ulcers are usually oval in shape but may be serpiginous The edge may have a clean cut punched out appearance or it may be rounded hard and fibrous it very rarely if ever shows the irregular undermined edge of the extending ulcer The mucous membrane in the areas between the ulcers is usually healthy

The les n f

of the muscular
l thickening of
ater there may
nal wall and a
lumen More
mucous mem

brane with polypoid formations

Blood —There is no characteristic blood picture There are two influences the tendency to microcytic anæmia as a result of repeated blood loss from the ulcers which may become an important factor and the tendency to a nutritional ... and/or dietary restriction patien ... ndition However in the uncompli ... may be almost normal There is

SYMPTOMATOLOGY

Clinical history — The con
dysentery but more frequently
most of which may have been re
they were inadequately treated
sufficient importance to them or
occurred

The **onset** may however be entirely spontaneous and without any previous history of bowel disorder

Symptoms —When the condition is fully established the patient will complain of more or less continuous discomfort in the abdomen which is less insistent after a period of rest and dietary restriction and is increased

after dietary (or alcohol) indiscretions, exposure to climatic extremes, especially cold, and subjection to physical, or more rarely mental, strain This discomfort is usually on the left side, over the descending and sigmoid colon, but it may be over the cæcum or at the flexures The pain may be partly relieved by defæcation or passage of flatus, but it rapidly returns It is more noticeable shortly after food is taken

The patient is always in a state of sub-health, and is easily tired, during exacerbation he feels definitely ill He is often slightly anæmic, has an unhealthy 'muddy' complexion, and his skin is inelastic He is often considerably emaciated, with a thin abdominal wall, *through which* the thickened bowel can be felt easily There are points in the abdomen which are constantly tender

A low pyrexia is common, this will amount to definite fever now and then, but usually the evening temperature is between 99° and 100°F

The number of stools varies, but, except during the occasional periods of constipation, they are seldom less than three, or more than five or six, ... They may ... of constipa- ... the formed or semi-formed stool

... toxic, and ... there ... erative ... driacal, ... a very

... diag-nosis from the history and examination of the patient, ... frequently very typical

The stools will often contain blood mucus and pus, and under the microscope they will show a cellular exudate and red cells

Sigmoidoscopic examination is, however, almost essential for satisfactory *confirmation of the* diagnosis Typical ulcers will be seen in a relatively healthy mucous membrane, some of these will probably be healed, others breaking down They usually bleed readily

The opaque enema (by the use of thin well diluted barium, administered slowly under low pressure into the previously prepared bowel) shows diminution or loss of haustration of the colon, at a later stage, the colon develops a smooth ... areas of narrowing ... *after its evacuatio*... involvement, and

TREATMENT

Once the diagnosis has been made, the patient should be made to realize that the treatment is bound to be very prolonged, and needs his (or ... operation and patience

hourly from 6 a m to 6 p m for a few days ... brings down the large bowel of mucus and debris It also frequently brings down the temperature During this period, the diet should be restricted to fluids, *e g* milk, which may be *citrated or peptonized*, butter milk, chicken broth, and fruit juice Sometimes, considerable improvement can be effected by

giving by mouth some of the recognized arsenic or iodine preparations used in the treatment of amœbic dysentery (*q v*), and recently we have had

Colonic irrigation —Many drugs have been recommended eusol, chiniophon vioform sodium sulphapyridine and several organic silver preparations but the writer has found silver nitrate as satisfactory as any of these more expens dr s

bowel washes should be run in through a soft catheter under low pressure (18 inches to two feet of water)

e solution should be 1 in 1 000 at first stages to 1 in 750 1 in 500 1 in 400 If on any particular day the enema is it with normal saline

The patient should be encouraged to retain the medicated enema as long as possible up to five hours These washes should be given daily or f the

free diet by rapid stages The diet must contain adequate protein in some easily digestible form and all the vitamins and minerals but it must include only the minimum of residue Plenty of fluid and adequate salt r

G

by m

possi

laxatives should be taken

The anæmia should be treated with suitable hæmatinics as indicated by the blood counts but very often it will be advisable to give both liver and iron In severe cases a blood transfusion will often initiate a period of improvement Sedatives analgesics and antispasmodics may be required it may be advisable to give a bromide mixture for a week or so at the outset and at night in order to

latter in the form of D

Progress —Except

treatment too soon even after an apparent complete cure a relapse is very liable to occur unless great care is taken regarding the diet in particular, for months or even years

On the other hand, if the patient does not improve after two or three months' treatment, and after several changes of bowel wash, surgical treatment will have to be considered Two operations are recommended, appendicostomy and ileostomy, by the former, a means of giving efficient bowel washes is provided, and by the latter the fæcal matter from the upper bowel is side-tracked as well The latter is undoubtedly more efficient, but the former is simpler to do, and much simpler to undo when it is no longer required Care should be taken not to resort to surgery too late, because once the large intestine has become fibrotic, it will contract with disuse, and become a hard narrow tube that will never function again properly, and a permanent colostomy will be the result

Prognosis —This will depend on how early the treatment is undertaken, and on the vigour and skill with which it is prosecuted, this in turn *will depend on the co-operation of the patient, and on the circumstances in* which he is placed

If proper treatment is undertaken early, cure should always be possible, but many neglected patients have passed into a stage of chronic *invalidism, while other have gone rapidly down hill, and have died of* exhaustion or intercurrent disease within a few months

Addendum —Stannus (1943)* has developed a very attractive theory on the ætiol ogy of sprue He *considers that the primary physiological lesion in sprue is a*
' that this is determined
This defect he believes
nplex possibly including

The present writer's hypothesis that behind the *ætiology of sprue there is an* inborn error or 'weakness of metabolism seems to tie in well with Dr Stannus's hypothesis except that in the former there is less emphasis on the specific dietary deficiency and more on the constitutional factor

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* Stannus *H S (1943) Sprue Trans Roy Soc Trop Med & Hyg 36* 123

SPRUE

Introduction —Most of the early writers on sprue emphasized the fact that the disease was confined to Europeans or persons of mixed European and Asiatic descent It has long been recognized that the incidence in different racial groups is in inverse ratio to the degree of pigmentation of their skins There is, however, a natural tendency to report the rare case, so that the exceptional cases of sprue in Indians or other indigenous inhabitants of the tropics have received greater publicity than the ordinary run of cases in Europeans, with the natural consequence that the undoubted

not receiving sufficient emphasis in

r has not yet seen a typical case of

that typical cases do occur amongst

There occurs, however, commonly amongst Indians a now-well-recognized syndrome of macrocytic anæmia, nutritional in origin, that is often associated with a chronic watery diarrhœa In some of these cases, there are certain signs and symptoms that are also typical features of the sprue syndrome, for example, emaciation and a sore, red and glazed tongue In fact many of these cases in Indians would pass as modified sprue, and are often diagnosed as such

There is also a condition of chronic watery diarrhœa, with perhaps a slightly sore tongue but at first without macrocytic anæmia, that occurs amongst both Europeans and Indians and is usually referred to as 'pre-sprue' The name is not a good one, as, even if one does not take the view that true sprue never occurs in Indians, the name implies that sprue must inevitably follow unless the condition is cured This is not the case, for, although many patients with sprue give a history of previous diarrhœa, this diarrhœal condition referred to here may continue for many months and even years without the patient's developing further typical symptoms of sprue, but emaciation, a sore tongue and a macrocytic anæmia are common sequelæ, so that the condition develops into the malnutritional syndrome described above as commonly occurring in Indians For this condition the writer has for some years used the word 'para-sprue'

While there are undoubtedly all degrees of conditions between (*a*) nutritional macrocytic anæmia, with or without diarrhœa, (*b*) para-sprue, and (*c*) true sprue, the writer believes that they are not just stages of the same condition, but that para-sprue and sprue have different ætiologies, just as they have distinguishable clinical pictures The conditions are therefore described separately

Definition —Sprue, or psilosis, is a diarrhœal condition of uncertain ætiology, characterized by emaciation, the passage of large, light-coloured and frothy stools with a high fat content, flatulent dyspepsia a sore tongue, a low glucose tolerance curve, and eventually a marked macrocytic anæmia occurring amongst people who live, or have lived, in certain tropical countries

Historical —Early historical records of this still not very clear-cut syndrome are not very clear and it is obvious that ma
refer to other diarrhœal diseases Manson B
tions of Ketelaer in 1669 and of Hillary in
name was first used in the descriptions of
in Java in 1879 and 1880 respectively

Recent contributions to our knowledge of this disease have been more destructive than constructive for example Thaysen (1931) and later Mackie and Fairley (1934) showed that our previous conception of the morbid anatomy of the disease was entirely erroneous

EPIDEMIOLOGY

Geographical distribution —'Sprue' without any qualification usually ... 'tropical sprue', but there is little question that there is an indis-

tinguishable condition which occurs amongst persons who have lived all their lives in a temperate climate, to this the name 'non-tropical sprue' is usually given Some 170 cases of non tropical sprue have been described, these reports have come from several countries, mainly the U S.A and Great Britain

Tropical sprue is most commonly associated with residence in China, India Ceylon, Malaya, the East and West Indies, southern U S A Central and South America, southern Italy, and Queensland, that is to say it is for the most part truly tropical, but a few sub-tropical areas are included, and the disease is rare in tropical Africa Its realm lies between 40°N and 20°S

Age and sex —It is more common in females than males, and is essentially a disease of middle age, but it may occur in young people and even in children

ween skin pigmentation and sprue
has is commonest amongst European
and ongst Chinese Malays, and fair
nort rk southern and eastern Indians,

attacks of hill diarrhœa

Seasonal —The onset is usually after or during the rains

Other epidemiological observations —Sprue houses in which a succession of residents have suffered from sprue have been reported, and this has led to theories regarding its infectious nature also, husband and wife not infrequently both suffer from the disease It has been specifically associated with heavy white-ant infestation of the house and with dry rot, neither being very unusual associations in the tropics

Time relation to tropical residence —It is usually associated with long tropical residence and it is common in the domiciled European in tropical
sojourne
this has
means u

ÆTIOLOGY

(i) Sprue has a definite incubation period of usually three to six months after residence in the tropics
(ii) The geographical distribution is patchy and peculiar
(iii) Evidence has been collected that several members of the same family

In the Plummer-Vinson syndrome, the throat is usually affecte anæmia is microcytic and except the low gastric acidity, other t

absent and usually the emaciation

Fatty stools—(Cœliac disease and 'non tropical' sprue are i cluded here as we consider them analogous to 'tropical' sprue, as ha indicated above) In pancreatitis or pancreatic tumour the unsp is increased at the expense of the split fat and there may be sugar urine

by the therapeutic test

Low glucose absorption curve—This is not very uncommon in individuals, and may be very marked in para sprue (*q v*) common in sprue it is not a very helpful differential diagnostic poi

it
e
a

per cent of cases of sprue pernicious anæmia will be excluded by the of some free acid

appearance will be f (Mackie and Pound 1 or duodeno colic ana

TREATMENT

Introduction—It has been said of sprue that there are 365 i cures It is easy to understand the multiplicity of the specifics, sin are so many deficiencies that go to make up the sprue syndrom rectification of any one of these may go a long way towards resto

There is thus no short cut to treatment of this condition patie be warned that their whole hearted co operation is essential and t must be prepared to face a period of at least two months of ho the equivalent treatment

The treatment consists of rest in bed a strict dietary regi treatment for the anæmia and gross deficiency conditions, otherw symp liver of th be gi

provement in the blood picture and also in the general condition, but en in the cases in which anæmia is the most prominent symptom, this atment alone is seldom sufficient Those reported cases in which liver atment alone was effective were probably not true sprue but para sprue nutritional macrocytic anæmia

Diets

Rationale —The object of the dietary is to rest the disorganized fat and rbohydrate digestive mechanism and at the same time to ensure proper trition to the tissues This is best done by giving a high protein diet th a sufficiency of all the vitamins and essential minerals and at the same ne restricting the fat and carbohydrate intake

If this principle is observed the details are not of very great impornce and the diet will certainly have to be varied according to the circumances under which the patients are being treated as well as from patient patient

The ratio of protein fat carbohydrate in a normal diet is 1 1 5 a sprue diet, the proportions of fat and carbohydrate must each be

h milk By
very nearly
ut obtaining

u able milk, sprulac , a proprietary (Cow and Gate) preparation of dried ilk with an exceptionally low fat content (P = 1 0 F = 0 3 C = 1 3), ould be given

The five stages of this milk diet are given in table X below The eds must be taken every two hours from 6 in the morning until 8 at ght with an extra milk feed at 2 o clock in the morning if the patient is vake this makes 8 milk feeds and one fruit meal the latter in the middle the day The milk must not be drunk from a cup but sipped from a

milk but this difficulty is
nilk *e g* by peptonization
of butter milk or some

Table X

Stages	1	2	3	4	5
I lk sk mmed pints	3	4	5	5	4
whole				1	2
ru t* ounces	8	8	8	8	8
lucose ounces	1	1	1	1½	2
ggs				1	2
utter ounces					½
u ks* ounces		1	2	3	3
alories	846	1 166	1 480	1 986	2 412
Proportions					
rote ns	1	1	1	1	1
ats	0 1	0 1	0 1	0 3	0 5
arbob drates	2 2	2 2	2 2	2 3	2 5

* *See* footnotes to table XI

Showing the dietary items, their quantity, their protein (P), fat (F) and carbohydrate (C) content, and their calorie value, in the five stages of the sprue diet

Stages	I					II					III					IV					V				
Article of food	Oz	P	F	C	Cal	Oz	P	F	C	Cal	Oz	P	F	C	Cal	Oz	P	F	C	Cal	Oz	P	F	C	Cal
Skimmed milk	48	48	5	67	505	60	60	6	84	630	60	60	6	84	630	40	40	4	56	420	20	20	2	28	210
Whole milk																20	18	22	28	382	40	36	44	56	764
Fruit* (orange juice)	8	2		22	96	8	2		22	96	8	2		22	96	8	2		22	96	8	2		22	96
Glucose	1			30	120	1			30	120	1½			45	180	2			60	240	2			60	240
Chicken						4	34	8		208	4	34	8		208										
Rusks†						1	2	2	21	110	1	2	2	21	110	2	4	4	42	220	2	4	4	42	220
Liver soup						4	12	1	3	69	8	24	2	6	138	8	24	2	6	138	8	24	2	6	138
Fish											4	22	5		133	8	44	10		266	8	44	10		266
Lean meat‡ (beef)																4	30	14		246	4	30	14		246
Egg (boiled)																1	3	3		43	1	3	3		43
Biscuit (plain mild)																1	3	4	21	132	2	5	8	43	264
Butter																¼		6		54	½		12		108
Liver (lightly cooked)																					4	24	3	3	135
Total ..		50	5	119	721		110	17	160	1,233		144	23	178	1 495		168	69	235	2,237		192	103	260	2 730
RATIO P F C		10	01	23			10	02	14			10	02	12			10	04	14			10	05	14	

A cup of weak tea with skimmed milk with glucose (or equivalent amount of sugar) from the ration can be taken once in the second and third twice in the fourth and three times in the fifth stages

Notes * *Fruit* Orange grape and grape fruit juice and mashed bananas papaya bael fruit and apple have been those most used by us but some other fruits *e g* strawberries if and when they can be obtained are suitable

† *Rusks* are bread baked in an oven until crisp one ounce of bread will make about 2/3 ounce of rusk

‡ *Meat* (beef or mutton) must be lean and raw it should be cut into very thin slices and cooked for *not more than one minute* in a double saucepan or in a thin frying pan over a saucepan of boiling water The meat becomes a light brown colour and loses its raw appearance and taste

If the nurse is preparing the meal it is only necessary for her to place the thin slices of raw meat (or liver) on the plate on which it is to be served and to place the plate over a saucepan of boiling water for about three minutes

The meat or liver can be cut up and eaten or it can be minced in the latter case salt pepper and marmite should be added and if a dry meal is preferred about half an ounce of rusk crumbs (from the ration) should be mixed with the mince

proprietary preparation such as Benger s food bovril added to milk will provide a change

If sprulac is used it must be given as follows —

First stage 6 ounces of sprulac (125 calories to the ounce of dry

added

hich is basically of milk, but added will usually be found lines that we have used for eight meals should be taken during the day and the patient must be given an exact programme to follow

Meat diet —The high protein diet recommended by Fairley consists largely of beef good quality beef is difficult to obtain in many trop cal countries and further to many patients beef is not only an unpleasant food but does not seem to su t them even if they can be persuaded to take it However many pat ents come under treatment in a temperate climate and this diet has certainly been very successful in its originator s hands

Fairley (1939) recommends the following diet —

TABLE XII

HIGH PROTEIN MEAT DIET

D et No 1 (calor e val e = 770)

8 *a m* —Underdone beef 3 oz rusk ½ oz ju ce of ½ orange and glucose 2 d acl ms

12 *noon* —Soup 4 oz + liver extract (= ⅛ lb) underdone beef 3 oz rusks ½ oz ju e of ½ orange and gluco e 1 drachm

6 *p m* —The same as at 12 noon

Protein fat carbohydrate — 1 0 0.3 1.2

Note —When pat ents are very ill two hourly feed of meat and beef ju ce can be subst tuted

D et No 2 (calorie alue — 1,250)

8 *a m* —Underdone beef 5 oz ru ks 1 oz calves-foot jelly 2 oz ju ce of 1 orange + glucose 2 drachms

12 *noon* —Soup 4 oz + l ver extract (= ⅛ lb) unde done beef 5 oz rusks 1 oz ju ce of 1 orange + glucose 2 drachms

4 *p m* —Tea 10 oz m lk 2 oz

7 *p m* —The same as at 12 noon + cal es-foot jelly 2 oz

Protein fat carbohydrate = 1 0 0.3 1 0

D et No 3 (calorie alue = 1,820)

6 *a m* —Tea 10 oz m lk 2 oz

8 *a m* —Underdone beef 6 oz ru ks 1½ oz cal es-foot jelly 2 oz ju ce of 1 orange + glucose 2 drachms

10 *a m* —1 baked apple custard 1 oz

12 *noon* —Soup 4 oz + l er extract (= ⅛ lb), nderdone beef 6 oz calves-foot jelly 2 oz ru ks 1½ oz ju ce of 1 orange + glucose 2 drachms

4 *p m* —Tea 10 oz m lk 2 oz baked apple 1 oz cu tard 1 oz

7 *p m* —The same as at 12 noon

Protein fat carbohydrate = 1 0 0.32 1.3

D et No 4 (calorie v lue = 2,200)

6 *a m* —Tea 10 oz m lk 2 oz

8 *a m* —Underdone beef 6 oz rusks 1½ oz calves-foot jelly 2 oz ju ce of

10 *a m*—1 baked apple + custard, 2 oz

12 *noon*—Soup, 5 oz + liver extract (= ½ lb), underdone beef, 7 oz, calves-foot jelly, 2 oz, rusks, 3 oz, juice of 1 orange + glucose, 2 drachms

4 *p m*—Tea 10 oz, milk, 2 oz, 1 baked apple, custard 3 oz

7 *p m*—The same as at 12 noon, but only 1½ oz of rusks allowed

Protein fat carbohydrate = 1 0 0 34 1 3

Diet No 5 (calorie value = 3 020)

6 *a m*—Tea, 10 oz, milk 2 oz, glucose, 2 drachms rusks 1½ oz butter, 1 drachm, one scraped ripe apple or one fully ripe canary banana (yellow ends)

8 *a m*—Underdone beef 7 oz rusks 3 oz, calves foot jelly 2 oz juice of 1 orange + glucose, ½ oz, honey, 2 drachms, butter, 1 drachm

10 *a m*—1 baked apple, custard 3 oz

12 *noon*—Soup 5 oz + liver extract (= ½ lb), underdone beef, 7 oz, calves-foot jelly, 2 oz, rusks 1½ oz, juice of 1 orange + glucose ½ oz

4 *p m*—Tea 10 oz, milk 2 oz, glucose 2 drachms, rusks 3 oz, baked apple 1 oz, custard 3 oz (egg boiled or poached sometimes substituted), honey, 2 drachms

7 *p m*—The same as at 12 noon

Protein fat carbohydrate = 1 0 0 36 2 0

Routine —The patient must be confined strictly to bed during the first few stages of the treatment, as bodily and mental rest are as important as in the treatment of duodenal ulcer, for example If possible, the patient should be in an institution and should also have a special day nurse unless the institution is very well staffed If treated at home, he must have a day and a night nurse, and the former should be carefully selected, and, if possible, should have had previous experience of sprue

The first stage of the diet should be adhered to for at least ten days, [illegible]

one, back to the first stage

The patient may be allowed to get up for defæcating and washing during the fourth stage, and to sit up in a chair for part of the day during the fifth stage

The injections of liver extract (the whole liver extracts are usually better than the more refined ones, and they must be given in generous dose [illegible] be given daily [illegible] paration, and vitamin-A and [illegible] and additional calcium in the form of calcium lactate or basic triple phosphate in doses of a drachm thrice daily

Cortin appears to aid fat absorption in some cases, and should be given a trial

Symptomatic treatme[illegible] ment of treatment, a full [illegible] any tendency to constipat[illegible] in the *bazar* in India, or [illegible] should be given regularly [illegible] in preference to liquid [illegible] effective absorption of vitamins The atonic condition of the bowel may have led to a constipated condition in which there are large fæcoliths in the bowel that may necessitate warm oil enemata for their removal

It is probably not advisable to interfere too much with the looseness of the bowels if it occurs in the early stage before treatment has had time to take effect, but later, if the diarrhœa is troublesome or distrubs [illegible] kaolin or bismuth should be given A course of

sulphapyridine produces surprisingly satisfactory results in some cases of obstinate diarrhœa

water after meals

When there is gross emaciation intravenous glucose, 200 c.cm of a 25 per cent solution of glucose together with 10 units of insulin and for cramps or tetany parenteral calcium and parathyroid by mouth, should be given

chlorate mouth wash a drachm to the pint or optochin should be used or if the mouth is painful glycerine and borax, with 2 grains of cocaine to the ounce in extreme cases when the soreness is interfering with the taking of nourishment

Convalescence —Exercise must be graded carefully and the patient should not be allowed to return to full work for two or three months 'Home' leave is the ideal solution if it is during the summer but an

The question

If he has

L DIARRHŒA)

ite is within

t depend on

whether the food and accommodation will ... to be entirely satisfactory

this that individual should be recommended to return to a temperate climate where for some time he may still have to consider his diet The long continuance of restricted diet is also a precipitating factor and must be guarded against If such a diet is inevitable, then extra vitamins must be given

Prognosis —This is dependent on the stage at which the patient comes under observation the co operation of the patient and the facilities for proper treatment If the treatment is undertaken early the prognosis should be good but it may be necessary for the patient to leave the tropics, this is particularly the case if the symptoms developed after short residence as it will indicate that the patient is particularly predisposed to the condition

At the other end of the scale if a patient is grossly emaciated with a distended abdomen has serious macrocytic anæmia and is unable to take

solid food on account of extreme soreness of the mouth, the prognosis is grave, but not hopeless if conditions for treatment are optimal

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PARA-SPRUE

Definition —Para sprue is a disease of dietary origin in which there is a watery diarrhœa of long duration, loss of weight, a sore red tongue, and later marked macrocytic anæmia, it occurs in the European sojourner, the domiciled European and Eurasian, and the native in the tropics

ÆTIOLOGY AND EPIDEMIOLOGY

patient is kept on a low fluid diet for a long time, it is found amongst pregnant women (Napier and Edwards, 1941) It also occurs in poorer-class Europeans and Eurasians and in economically-higher classes of these two groups following long continued bowel disturbances

PATHOLOGY

Little is known of the morbid anatomy of this condition

4 per cent of normal persons

Stools —They are usually watery and light in colour, but not the bulky, frothy and pale stools of sprue, there is often some increase of fat, but the total fat is seldom above 30 per cent of the weight of dried fæces, with the normal proportion of split fat

SYMPTOMATOLOGY

The onset is usually gradual, following a period of ill health as indicated above In the fully-developed case, there is emaciation a sore red tongue, sometimes a low fever anæmia with its accompanying signs and symptoms, and diarrhœa without any localizing abdominal symptoms There is also usually dyspepsia, flatulence, and abdominal discomfort

or of some concomitant infection

Diagnosis —There is no clear cut method of diagnosis The absence of the extre
men, the p
pale stools
the absence
Ulcerative
exudate in the ... have to be
considered, in ... be found by
examination of ... nal inocula-
tion of an anti ... l usually be
occult blood

TREATMENT

The treatment of para sprue is very
strict dietary regime is necessary We
take the full mixed hospital diet (whic
possible, supplemented by eggs extra milk and marmite While it is un-
ken that the meat is not
to serve it and in fact,
id serving of the food
specific item and this
should be given in full doses of one of the whole liver (or crude) extracts. The blood picture improves immediately, with a sub maximal reticulocyte response

For the diarrhœa treatment for not more than two days with sodium sulphate in drachm doses four hourly is followed by kaolin or a bismuth mixture if necessary until it stops but quite often the stools will become

the new, less soluble drugs, such as sulphaniiyl guai ...
efficacious
... chloric acid should be given with each
iated infections, particularly
For anæmic patients a blood
beyond that of simple blood
replacement

Prognosis —With adequate treatment this is usually good and if the response is not rapid one should question the diagnosis, and again consider such conditions as ulcerative colitis or intestinal tuberculosis

HILL DIARRHŒA

DISCUSSION —The literature on hill diarrhœa goes back nearly a hundred years it presents a kaleidoscopic series of pictures of the possible or probable ætiology of this condition which all seem totally disconnected, each writer s contribution being mainly destructive of previous theories and presenting very little in the way of constructive contribution to the problem Some of the theories that were put forward were that it was a form of scurvy—even at that time (1854) known to be due to lack of fresh fruit and vegetables that it was a disorder of the liver due to the low tempera- [illegible]

station Nearly all hill stations are appallingly insanitary and much of the diarrhœa is due to mild *Bact flexneri* infections acquired through water, milk or food particularly the latter which is usually infected by flies The [illegible] the early writers and which fre- [illegible] us nature of the disease Another

of case which does not quite fit any of these suggested ætiologies namely

[illegible] and this patient does not suffer in the same way when he returns to a cold climate in Europe This only constitutes a very small percentage of the cases of hill diarrhœa, but the writer believes that such

demand for the raw material for additional blood formation might lead to a lower rate of wastage and again decreased bile formation Decreased bile will lead to a
condition of the bo
varies, so that th
than in others

Symptomatology.—This will naturally vary according to the cause The usual experience is a watery diarrhœa, which starts very soon after the patient reaches the hill station, and is accompanied by mild constitutional symptoms, microscopical examination shows a cellular exudate but seldom any blood, suggesting a mild bacillary dysentery

In true hill diarrhœa—if there is any such condition caused by the climatic effects only and the writer believes that there is—the stools are very similar to those of sprue, the main defect is an increase of fat which in some cases is associated with a deficiency of bile There will be a large fluid, f
up to
There
arrivals at a hill station—and a certain amount of lassitude, but otherwise the subject does not feel particularly ill, and he is able to enjoy, but not to the full, his holiday, or to carry on his work, as the case may be

Treatment—The treatment of the infective type is with sodium sulphate in 2-drachm doses every four hours during the first day or two, followed by kaolin or bismuth, as in mild forms of bacillary dysentery More severe forms may require sulphapyridine or sulphanilyl-guanidine

hydrargyri perchloridi, thr
pepsin two hours later

LEPROSY

by

John Lowe M D

Introduction —In the last two decades it has become increasingly realized that in different countries there are marked variations not only in the incidence but also in the *severity of leprosy* In some countries *e g* parts of India and of Africa leprosy is very common but often mild In other countries *e g* parts of the Philippine Islands and of South America the disease is less common but considerably more severe In still other countries *e g* parts of South China, of Burma, and of South America, the disease is both common and severe

An unbalanced and depressing view of leprosy may be the result of studying leprosy in countries where the disease is usually seen in severe forms, and particularly when such studies are largely confined to severe cases seen in leprosy institutions. Such studies appear however not infrequently to have formed the basis of accounts of leprosy in medical literature.

The description of leprosy given here is based on long experience of leprosy in the general population of India, supplemented by experience gained in brief visits to other countries, and by a thorough study of the literature of the disease.

In most parts of India, the milder neural type of the disease predominates, and slight abortive cases of leprosy are common, even the cases of the severer 'lepromatous' type are frequently less severe and progressive than those seen in some other countries. It will, therefore, be found that the picture of leprosy presented here is on the whole less depressing than that frequently presented in medical literature. The disease is *not* described as highly infectious, nearly always progressive, and sooner or later but invariably fatal.

It is however believed that the description given here can be applied, with minor modifications, to leprosy in any country, and that probably nowhere in the world is the prognosis of leprosy so hopeless as is often suggested.

Definitions.—Leprosy (Synonyms.—Lepra Elephantiasis Graecorum, Lepra Arabum) is a disease belonging to the group 'infective granulomata', is caused by *Mycobacterium lepræ*, and is transmitted from man to man, mainly if not entirely, by [illegible] tropical and sub tropical [illegible]

[illegible] mild, and the lesions are confined to certain areas of skin and/or to certain peripheral nerves and the tissues supplied by them. The **lepromatous type** is relatively severe and progressive, and the lesions are usually widespread in skin and mucous membranes, and to a less extent in the internal organs, the vital organs however show little or no affection.

The definition of these two main types of leprosy adopted at the International Leprosy Congress, 1938, was as follows:—

> *Neural (N) type.*—All cases of the benign form of leprosy with disturbances of polyneuritic nature (*i.e.* alterations of peripheral sensation, trophic disturbances, atrophies and paralyses and their sequelæ) or macules of a non-lepromatous nature (*i.e.* leprides usually with localized sensory disturbances) or both. These cases give evidence of relative resistance to the infection, are of relatively good prognosis as regards life although mutilation may take place, and usually react positively to lepromin. Bacteriologically the skin lesions are typically but not invariably found negative by standard methods of examination, though the nasal m[illegible] ...e histologically of [illegible] form of leprosy. [illegible] lepromin exhibit- [illegible] the nerve trunks. [illegible] Disturbances of [illegible] ...ally absent in the earlier stages and present in the later stages of primarily lepromatous cases, and often present in cases arising secondarily from the neural form.*

Some of the points made and the terms used in these definitions are later explained more fully.

* In our experience the nasal mucosa in true neural cases shows no bacilli.

HISTORICAL

Leprosy in ancient medical writings—The earliest references to leprosy confirmed by clinical descriptions are in the ancient literature of India, the *Sushruta Samhita* (about 600 B C) contains definite references to, and descriptions of, leprosy but there are other probable references in still older Indian literature The supposed references to leprosy in ancient Egyptian, Jewish, and Chinese writings of the pre Christian era are of doubtful authenticity, no definite clinical details indicating leprosy being given, but this fact does not prove that leprosy was not prevalent in ancient times in the countries in question In most ancient medical

generally used for leprosy, originally meant skin disease in general, the Greek word *lepra* ' from which name ' leprosy ' is derived, originally meant a scaly disease, possibly psoriasis, and was only later applied to leprosy, as the result of mistakes in translation

The disease was possibly mentioned by Hippocrates, and certainly mentioned and described by later Greek writers, Lucretius, Celsus in the first century B C , and by numerous later authors in Greco Roman times These writers first mention leprosy as a disease rare in Italy but more common in the eastern Mediterranean Later, the spread to Italy and to other parts of Europe is recorded by contemporary writers

With the collapse of the Greco Roman civilization the science of
'y forgotten in Europe, but the Greek
the Arabians, who studied the Greek
leprosy, and wrote extensively them-
writings on leprosy were recovered to
Europe first indirectly from the Arabian writers by the writers of the school of Salerno in Italy in the tenth century, and, later, directly through the recovery of the ancient Greek writings themselves

During this time the terminology of leprosy became confused, and it took many centuries to clear up this confusion

Both the Greek and the Arabian writers had used both the terms *lepra* and

The medical writings on leprosy in Europe in the Middle Ages were dominated very largely by the Greek writings, and contain little original material Dozens of descriptions of leprosy were, however, written in the countries of Europe Under the impression, possibly a mistaken one
(Old Testament Hebrew) and the *lepra* (New Testa-
lieval Europe
(but not all)
was applied
to the medieval leprosy

Leprosy in modern medical writings—The developments of scientific and medical knowledge which later followed the Renaissance were not for a long time applied to a study of leprosy, partly because by that time there was little leprosy left in Europe It was only in the nineteenth century that the Norwegian workers Danielssen and Boeck, and later Hansen made the studies which led to the scientific work on leprosy,

especially in the last forty years This work has established leprosy as a disease showing many points of resemblance to tuberculosis, and also some important differences

To the modern literature of leprosy, workers of many nations have made notable contributions

— d in Norway by Danielssen and Boeck later by Lie and others Other workers Among Ehlers Marchoux Jadassohn Radcliffe-Crocker, Paldrock Tonkin

Numerous United States workers have studied leprosy in America, Hawaii or the Philippine Islands amongst these workers are included Dyer Hopkins Denny Dean Hollman Macdonald Heiser McCoy Aycock McKinley Soule Wayson Wade Cole and Hasseltine

In the Philippine Islands Filipino workers include Rodriguez, Lara Nolasco Manalang and Chiyuto

In India organized leprosy research was initiated by Rogers and carried on by Muir Later workers include Chatterji Cochrane Dharmendra Henderson Lowe and Santra

In Japan leprosy workers have been very numerous and have included Sugai Ota Sato Asami Mitsuda Hayashi and Uchida

In South America in recent years leprosy work has much developed and among the writers have been De Souza Araujo Balina Fernandez Fidanza Schujman De Souza Campos Rotberg and Rebello

In the French colonies have worked Delinotte Tisseuil Montel and others in the Dutch colonies de Langen Lampe and Sitanala and in the Belgian colonies Dubois Degotte and Radna

In Australia workers have included Ashburton Thompson Cilento and Molesworth in South Africa Moiser Mitchell and Strachan

In other parts of the British Empire Frazer and Ryrie (Malaya) Rose (West Indies) Simon (Ceylon) and Austin (Fiji) have worked on this subject

In China workers have included Maxwell and in Korea Wilson

The writings of these and many other workers are largely contained or abstracted in *Lepra Bibliotheca Internationalis* (1900 to 1914) and the *International Journal of Leprosy* from 1933 These publications and also the other publications mentioned in the bibliography have been used in the preparation of the present chapter but it has been considered inadvisable to burden the text with hundreds of references A select bibliography is given at the end of the chapter

The history of the disease —This has already to a considerable extent been outlined in the preceding discussion Leprosy has been common in India, and probably in Africa and China for many centuries In classical times leprosy invaded the Mediterranean countries and later it spread over most of Europe including the British Isles For about a thousand years it was common in these areas and then between the fourteenth and sixteenth centuries, it declined markedly although it persisted and still persists in some foci in Europe chiefly in the countries bordering the Mediterranean and to a less extent in Iceland Scandinavia and the Baltic countries

The decline of leprosy in medieval Europe has been attributed to segregation measures to improved hygienic conditions and diet to climatic changes and to the development of racial immunity None of these

have very little leprosy

More recent still is the spread of leprosy to Australasia and the Pacif area Here Chinese immigrants have played an important part I Australia the disease has become endemic only in the north, chiefly i Queensland, but a few cases are found in other areas, both white an coloured people being affected

In the Pacific, within the last century, leprosy has assumed epidemi

accelerated, by control measures

The history of leprosy, therefore, is one of persistent endemicity ir many tropical and sub-tropical countries, with periods of invasion into temperate and even cold climates, these periods however being sometime of very long duration

ÆTIOLOGY

The causal organi

genus *Mycobacterium,*

and the fungi It is ro

microns, and in breadt

slightly curved, and it frequently shows in its protoplasm dark staining granules, which may be multiple and small, and distributed evenly along the length of the organism, or may be single and large, occupying either the middle or the end of the organism The bacillus is stained readily by the Ziehl-Neelsen technique, that is to say it is acid-fast, and it is gram-positive

In active lesions of the neural type, the bacillus is found, but often only with great difficulty In lesions of the lepromatous type, the bacilli are very numerous, and they show a marked tendency to occur in round masses, *globi,* which occupy large vacuolar spaces in the infected cells It is this characteristic which enables a distinction to be made between the tubercle bacillus and the leprosy bacillus in the tissues In other respects the

morphologically identical

injected bacilli c

where, but ther

generalization of the disease *It appears that, up to the present, the only* animal found susceptible to the organism is man Numerous attempts at experimental inoculation of human beings have been made, with positive

usually immune

Viability—In the circumstances outlined above, we have very little evidence regarding the viability of the organism, and it is impossible to say

st in a living
what condi-
urmise that it
by heat and
by drying

The
sually
with
most
highly
act
ertain
skin,
rough
mucous membrane

Congenital infection does not occur Infection *in utero* has occasionally been reported (at post-mortem examination) but it can very rarely be followed by the development of the disease, for children separated at birth from leprous parents practically always remain healthy The general opinion is that transmission by air, by food and water, by biting insects

It is
ditions
bacillus

important in preventive work

The idea has, however, occasionally
bacilli cannot be demonstrated in them,
Such ideas are usually based on the fac

not known as such to others In a recent epidemiological study carried on

in villages in one part of India in 80 per cent of the new cases arising during the period of the study infectious contact could be proved

Strong support of the view
afforded by a recent careful
Philippine Islands in which it
the family contacts of closed
of leprosy in the general population with no known contact while in contacts of open cases the incidence was *of course much higher*

IMMUNOLOGY

There is no doubt that the degree of natural susceptibility to leprosy in different persons varies considerably Under Epidemiology the various factors which may have an influence in this matter are discussed

There is also considerable evidence (*vide infra*) that acquired specific immunity to leprosy occurs but there is no completely specific test for such immunity There appears to be however a definite element of specificity in the lepromin test

The **lepromin test** was originated over thirty years ago by Mitsuda and consisted of the intra dermal injection of a minute amount of an emulsion made by grinding up lepromatous tissue rich in bacilli and previously sterilized by boiling A positive result is indicated by the development during the next few weeks of a small nodule at the site of injection A positive result is commonly seen in cases of the neural type particularly *tuberculoid cases in healthy contacts particularly adults* and in some healthy non contacts particularly adults A negative result is seen in cases of the lepromatous type and in healthy young children contacts or non contacts The completely negative result seen in cases of lepromatous type is a striking feature of the test and it is po ibly analogous to the negative result seen in some very advanced cases of tuberculosis

Numerous later workers particularly Dharmendra have introduced
improv
and re
shown
free fr
by weight

Recently Fernandez has shown and others have confirmed that the late nodular reaction is preceded by an early (24/48 hours) reaction of the tuberculin type which is of the same significance as the late nodular reaction It has moreover been found that by breaking down the bacilli by physical methods defatting and grinding the early reaction can be *enhanced and the late nodular reaction* can be almost abolished

has been much reduced without [illegible]
positive results in neural cases

There appear to be two factors contributing to a positive result in the [illegible] and the other non specific and so far it has been
factor Until this is done
gnosis
considerable In healthy
leprosy will
conta[illegible]

The incidence of leprosy in endemic areas and countries varies markedly It is noticeable that, compared with some other chronic infective diseases, the incidence of leprosy is never very high An incidence of more than 10 per cent of the population of an affected area is very rare and

In Burma, Bengal, Orissa, Madras and other parts of southern and eastern India, most of these areas being low lying, hot and humid, the incidence of leprosy is generally high, 0 5 to 3 per cent, and may be 5 per cent or more in certain areas In individual villages

of India, leprosy is relatively common

In other endemic continents and sub-continents for example Africa and South America

ing t
incid have revealed the following interesting facts regarding the type-distribution of cases In India, in areas where the incidence is high, most of the cases, usually 70 per cent and sometimes even 90 per cent or more, are of the neural type, often of the tuberculoid variety, and many are slight and abortive In contrast with this, it is found that in other areas, and commonly where the

Africa, sim
they are possibly
appear to predo countries, including Burma, the Philippine Islands, Japan, South China and also South America, lepromatous cases appear to form a high proportion often a much higher proportion

at different ages are
ig exposed to infection
r cent, while children
ence of 50 per cent or more These differences may not be entirely caused by the age factor Other possible factors are mentioned elsewhere

It is also suggested that, if leprosy is contracted early in life, it is more likely to take a serious form than if contracted later in life, but evidence on this point

Th hed in two ways In a few a incidence in different age-gro the population More often p a study of the age-distribution of the cases detected in surveys Here three age-groups are considered up to 15—the early age group, 15 to 34—the middle age-group, and 34 and over—the late age-group, these age-groups being chosen because in India they are of approximately the same size, and because accurate ages may be unobtainable

In most endemic areas, the largest number of cases, and sometimes the highest incidence, will be found in the middle age-group This finding, however, does not indicate the age when the disease is acquired, for leprosy is a very chronic disease with a long latent period Studies of the age of onset indicate that symptoms most commonly appear at the period a few years before and after puberty and, when the latent period is allowed for, it appears that most leprous infections are contracted in childhood or early in adult life

While the highest number of cases is generally found in the middle age group, marked variations are found both in the relative incidence and in the proportion of cases in the early and late age-groups The findings in this respect may vary in different countries and in different parts of the same country, and also may show some relation to the type-distribution which has already been discussed

In areas in which the severer lepromatous forms of the disease are common, leprosy frequently shortens life, so that the number of cases and the incidence in the late age-group is relatively low At the same time the infectiousness of the lepromatous cases is sometimes associated with
sy in children and young people In such
of the cases is found in the earlier age-
the late age-group
state of things found in areas where the mild neural type of the disease predominates These mild forms of the disease do not appreciably shorten life, and the result is an increase in incidence with increase in age, and a high proportion of the cases in the late age-groups Together with this the low infectivity of most of the cases is often associated with a relatively low incidence in children

There are of course areas in which the type-distribution and age-dis-

different countries but sometimes in different parts of the same country In some countries including many parts of India, the proportion of frank lepromatous to neural cases in the early age-group is low, and shows a relatively small rise in the later age-groups Such findings indicate that the disease is relatively mild and often not progressive

In other areas, however, the proportion of frank lepromatous cases in children may be higher, and in the later age groups lepromatous cases may be in the majority Such findings indicate that, in these areas, the disease is relatively severe and progressive

The importance of type- and age-distribution of cases is now being increasingly recognized, for crude incidence figures may give little indication of the public-health importance of leprosy in any area A high incidence, if associated with mildness of the disease, as shown by the figures for type distribution, and a low proportion of cases in young people as shown by the figures for age-distribution, may be considerably less serious than a lower incidence of leprosy in its severer form, with the infection of numerous young people

Sex incidence —Studies of leprosy in the general population have shown that, in most p
higher in men than in
is found even in chil
adult life Also females tend on the whole to show milder forms of the

disease The reasons for these differences are not clear The possible causes are an inherent lower susceptibility of females or a less degree of exposure to infection

The influence of heredity Race —There is considerable evidence to show that the severity and the forms of leprosy vary quite markedly in different countries and it has been suggested that some races are more susceptible to leprosy than others These suggestions have been borne in the same place for example, laya Indians and Burmans in West Indies and Europeans and workers No matter where the

ceptibility to leprosy of a race with the length of the period of endemicity in that race For example the Chinese among whom leprosy has been endemic for many centuries appear relatively highly susceptible to leprosy

tropics will very rarely get leprosy but when he does he will often get it in a severe form In the southern part of the United States particularly Louisiana the large Negro population in spite of relatively poor hygienic conditions shows a much lower incidence of leprosy than the population of European descent especially French and German These facts indicate that the postulated acquired immunity of European races if it was ever a reality may have died out since leprosy died out in Europe At any rate at the present time Europeans often show relatively little immunity Our knowledge of this subject however is very incomplete but it is clear that race is of importance

Familial susceptibility —From ancient times it has been realized that leprosy often runs along certain familial lines and this gave rise to the belief that leprosy was hereditary This idea has been disproved The possibility of susceptibility to leprosy being hereditary however has to be considered and a suggestion has frequently been made that in certain families certain persons exposed to infection develop the disease far more readily than persons of other families similarly exposed to infection and this suggestion is supported by a certain amount of evidence Accurate

An interesting suggestion has been made that the rarity of marital

If susceptibility to leprosy were truly hereditary it should be inherited according to Mendelian law and there is also a remote possibility that 'somatic linkage between this possibly hereditary factor and some other

easily recognizable hereditary factor might be found As Weiner points out, this can only be done by studying three generations of affected families and, as far as is known, this has not been attempted

The idea that leprosy is more common or more severe in persons of certain Landsteiner blood groups than in others has been suggested, but the author and others have failed to confirm this The blood groups are of course entirely hereditary The blood grouping of cases of leprosy of all types shows no significant difference from the blood grouping of healthy persons of the same population

It will be seen that definite evidence regarding familial susceptibility to leprosy is scanty, but it is a matter of common experience that some persons may acquire leprosy from very slight contact for a very limited period, the disease, sus- ceptibil

Th ship between sion on the hole, d it the disease High ociated with a low be of more impor- in detail, however, certain facts are revealed which are not in accordance with these ideas For example, in the very humid eastern part of Bengal, leprosy is considerably ern part of Bengal Dry central Burma than the more humid southern Burma iate is only one of a number of factors The fact that leprosy used to be common in temperate and cold climates indicates that a high temperature is not necessary for transmission, but the fact that infectious cases of leprosy imported into or repatriated to European countries, although often not isolated, very rarely give rise to secondary cases, indicates that, under cold countries rarely occurs climate on transmission, it the progress of the disease, in spite of the fact lisease of warm countries, it experience that persons suffering from leprosy in cold and hysically by a removal to a warmer bracing

During recent years, it has frequently been pointed out that, in Asia, the where rice is grown and forms direct causative rice areas may be caused more by climatic diet factor

A lack of salt has been mentioned in connection with a high incidence of leprosy, as well as the consumption of the toxic foods The idea has been advance of Colocasia antiquorum, of leprosy

ın many tropıcal areas but the evıdence to support thıs theory ıs of a very sımılar nature to and as completely unconvıncıng as the evıdence whıch Hutchınson quoted to support hıs fish eatıng theory of the causatıon of leprosy

Largely from analogy from other sımılar d seases such as tuberculosıs

than the consump

ıe spread of leprosy

e ın the ındıvıdual

ıat have been made

spread

ınfectıon ıs ıntroduced

PATHOLOGY

still recognizable, are often widely separated by whitish streaks of chronic inflammatory tissue These tissues may have undergone caseation and, where the areas of caseation are large, nerve abscess may be formed In chronic long-standing cases of the neural type, the nerve, instead of being thickened, may be thin and atrophic, and consist of little more than fibrous tissue

In the areas supplied by affected nerves, trophic lesions will often be found in ... of bones The only ... enlarge- ment of l... marked tuberculoid lesions

... ng to the clinical variety of ... In the '*simple*' variety of ... infiltration of the small round cell type, partly diffuse, partly peri-vascular and to some extent ... w as 'tuber- ... ically simple ... early lepro- matous changes

In lesions of the '*tuberculoid*' variety, whether in the skin, the cutaneous nerve, or the nerve trunk, the characteristic histological appearance is very similar to that produced by infection of the tissues with tubercle bacilli, hence the term 'tuberculoid'

The lesions consist essentially of small foci of epithelioid cells, often surrounded by areas of round cell infiltration, and often in the centre showing Langhan's giant cells and occasionally necrosis (It is this necrosis which causes the nerve abscess, and the ulceration of the skin patches occasionally seen) The small foci frequently coalesce and form large masses In these lesions, bacilli are usually relatively few, and may be very difficult to detect in smears or sections For some reason which is not clear, in the neural type of leprosy there is a marked tendency for these lesions to appear in the terminal nerve branches in the skin, from whence the changes spread up the subcutaneous nerves, and frequently cause marked lesions in the nerve trunks Hence the anæsthesia and nerve involvement in the neural type of leprosy

In the neural type of leprosy, these changes are found only in certain sites, namely, in certain areas of skin, in cutaneous nerves and nerve trunks, and sometimes in lymph nodes There is no similar involvement of the skin as a whole, or of the mucous membranes internal organs, etc

Lepromatous type **Morbid anatomy**—The changes in the skin are describe... the active phases of the disease the skin is ... and has a greyish white colour on section ... nd infiltration in the subcutaneous tissues Peripheral nerves may show thickening, usually of slight or moderate degree, over a considerable part of their course There is frequently a slight generalized involvement of lymph nodes and lymphatic vessels The alimentary tract is affected only at its upper end, with infiltra- ... f ... f

the liver and spleen caused by a chronic interstitial infiltration, and these organs may show a slightly irregular surface and a mottled appearance ... infiltration and enlargement, but ... shows little affection, the heart ... ly being normal, but the veins in

the affected tissues often show slight chronic inflammatory changes The

lepromatous lesions are found, their The tissues show interstitial infiltra- lls however being very different in character from those seen in lesions of the neural type The epithelioid cells are few and Langhan's cells are absent There is no marked tendency towards the involvement of nerve as compared with other tissues, most types of tissues being invaded The characteristic cell is the histiocyte in which the protoplasm frequently undergoes fatty change with the formation of vacuoles which may be filled with fatty material and masses of acid-fast bacilli ('foamy' cell of Virchow) In this type of lesion, bacilli are demonstrated in large numbers with great ease Such lesions are found in the skin, the nerves, the mucous membranes, the lymphatic glands, the bone marrow, and the internal organs

SYMPTOMATOLOGY

There is almost invariably a considerable latent period between the time when bacilli enter the body and the definite appearance of the signs of leprosy but it is only in exceptional circumstances that the time of the transmission of infection can be fixed with any accuracy In such cases, latent periods as short as a few weeks and as long as twenty years or more have been reported Some books describe **prodromal symptoms** with malaise, fever, rigors and pains in various parts of the body as commonly occurring before definite signs of leprosy appear and before diagnosis becomes possible

In the experience of the writer and he believes, of most other leprosy workers, such prodromal symptoms are very rare Such symptoms are not common even some time after clear signs of leprosy are evident Such reports suggest strongly that the diagnosis of the disease has been unneces sarily delayed until the disease has become generalized and reaction' has occurred

ountries such as India set is usually gradual a single initial slowly Some workers have is at the site of the sibility of some initial lesions being primary cannot be ignored In other patients, the lesions from the start are multiple Several patches may appear in various parts of the body, and slowly spread In other countries, and even in India in those persons who are more highly susceptible, the onset of the disease may be much more sudden and there may be a rapid appearance of lesions in many parts of the body, sometimes with malaise, pain in the limbs, fever, etc , cases with such an onset however are relatively few

Types of leprosy —Leprosy is usually a generalized or systematic infection, and the infection is rarely if ever confined entirely to one particular tissue (although in certain cases the recognizable lesions may be so confined) Clinically, however, leprosy shows itself in two main forms to which the term *neural* and *lepromatous* are now being applied The definition of these two main types of leprosy adopted at the International Leprosy Congress, 1938, has already been given The common clinical manifestations of these two main types are here described

NEURAL TYPE

The lesions seen in cases of the neural type can be divided into two varieties for which the terms *macular** and *anæsthetic* may be used

The macular variety (*see* plate XV) —There appear in the skin one or more patches usually clearly defined, round, oval, or irregular in shape, in which one or more of the following changes are found —

(*a*) Loss of pigment
(*b*) Diminution in cutaneous sensibility
(*c*)
(*d*)
(*e*) Dryness due to impairment of sweat function, scaliness, failure of hair growth, etc

The loss of pigment is usually not complete It may be more marked ... rythema, ... tised, by

... slight in ... *and most* ... itre may ... affected, ... of heat ... These sensory changes detectable by the physician are often accompanied by sensory changes described by the patient, such as feeling of hyperæsthesia, and formication, pain and tingling when the part is struck

The thickening of cutaneous nerves supplying the macule may not be easy to detect, although sometimes it is marked, particularly in cases with marked thickening of the macules Careful examination made with a knowledge of the distribution of cutaneous nerves will, however, not infrequently reveal nerve thickening, and this thickening may be traced from the patch up the cutaneous branches into the nerve trunks, which may also be thickened (*see* plate XVI, figures 1 and 2)

Thickening and erythema of the skin are often present in active macules, but they vary greatly in extent and degree They may be very slight, and affect only the extreme margin, they may be more marked, and affect the whole outer zone of the patch, they may be very marked and ... case they may be accompanied by scaling ... by actual ulceration Flat patches often ... r become flat again The thickening of patches may be very rough and uneven, and sometimes patches have a ...llated appearance (*see* plate XV, figures 2, 3, and 4)

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PLATE XV—LEPROSY NEURAL TYPE 'MACULAR LESIONS

Fig 1—'Simple' macule Flat pale slightly anæsthetic patches in a child
Fig 2—'Minor *tuberculoid*' lesion on the back Slight irregular thickening and erythema at the spreading margin Definite loss of sensation
Fig 3—Major tuberculoid lesion Marked irregular thickening and erythema of the *whole outer* zone of the patch Patch completely insensitive
Fig 4—Major tuberculoid lesion on the back The whole patch thick rough red, and completely anæsthetic



Fig 1



Fig 2





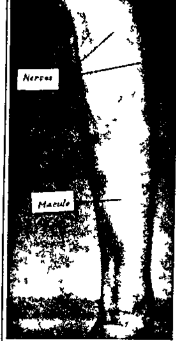


Fig 1



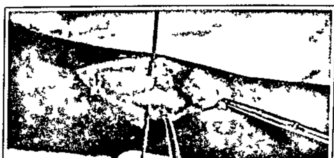
Fig 2



Fig 3



Fig 4



Sub classification of macular lesions —The International Congress on

previously been of this nature

The degree of tuberculoid change in these patches may be indicated by the terms *minor tuberculoid, tuberculoid* and *major tuberculoid* The tuberculoid variety of macular lesions is often associated with nerve involvement which may be great It should be emphasized that the different patches in the same patient are usually all of the same clinical variety

This sub classification is of considerable importance because the diff-

diameter) or very large (a foot or more in diameter) There may be only one
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Bacteriolog cal examination of these lesions usually gives negative results though sometimes a few bacilli are found and occasionally (usually during temporary phases of reaction) bacilli are fairly numerous

The anæsthetic variety —This form of neural lesion is characterized by the occurrence of leprous involvement of the peripheral nerve trunks This may arise as the result of an ascending infection spreading up the

(*a*) Impairment of cutaneous sensibility in the area supplied by the nerve starting peripherally and extending up the affected l mb

(*b*) Impairment of sweating and consequent dryness and scaliness of skin in affected parts

(*c*) *Pares s or paralysis with wasting of muscles supplied by affected nerves*

n of bones of hand
derlying bone which
infection of trophic
lesions

Perhaps the commonest nerves to be affected are the ulnar nerve the peroneal nerve and the posterior tibial nerve

PLATE XVI —LEPROSY NEURAL TYPE NERVE INVOLVEMENT

Fig 1—Thickening of cutaneous nerves supplying a patch on the forearm
Fig 2—Thick branches of cervical plexus supplying patch around the ear
Fig 3—Paralyses of 5th and 7th nerves Anæsthes a of cornea and inabil ty to close the eyes
Fig 4—Trophic ulcers of foot caused by tibial nerve involvement
Fig 5—Nerve abscesses of ulnar nerve exposed at operat on Two abscesses and markedly thick nerve between are seen

The affected nerve is usually thick, sometimes very thick, particularly the ulnar and peroneal nerves Sometimes the involvement of nerves causes nerve abscess (*v i*, and *see* plate XVI, figure 5)

The lesion of the ulnar nerve is most marked above the elbow, this lesion produces anæsthesia of the little and ring fingers, and on the ulnar side of hand and forearm, and later paralysis of small muscles of the hand, with the development of the typical deformed 'claw hand' of ulnar paralysis The peroneal nerve is often affected where it passes round the neck of the fibula The result is anæsthesia of the dorsum of the foot and of the outer side of leg, and paresis of the peroneal muscles with the development of 'drop foot' The posterior tibial nerve is commonly affected on the inner and posterior aspect of the ankle, and the result is anæsthesia and keratosis of the sole of the foot, and trophic ulcers (*see* plate XVI, figure 4)

Other nerves sometimes affected are the radial nerve, the median nerve, the fifth and seventh cranial nerves and the great auricular nerve The

orbital and facial muscles, ectropion, and lagophthalmos, with great liability to irritation of the eye by unfelt foreign bodies, conjunctivitis, corneal ulcer, etc (*see* plate XVI, figure 3)

In marked cases of the neural type of the anæsthetic variety, there may be anæsthesia of all the limbs and of most of the trunk and face, and paralysis, trophic lesions, and deformities in the arms, legs, and face

or tuberculoid, and the nature, significance and the course of the nerve trunk involvement are likely to be the same as those of these patches

permanent disability caused The less marked forms of nerve thickening are more likely to be of 'minor tuberculoid' or 'simple' nature, with less immediate damage but a greater tendency to chronicity and extension, and even to lepromatous development

The neural type in general —The chief clinical manifestations of the neural type of leprosy have been outlined Both types of lesion, macular and anæsthetic, may be present in the same patient For practical purposes, in cases of the neural type, we may regard the infection as being confined to the macules in the skin and to the affected cutaneous nerves and nerve

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PLATE XVII —LEPROSY NEURAL TYPE TUBERCULOID REACTION AND SPONTANEOUS SUBSIDENCE

...eration of tuberculoid lesion on face ...ischarge Complete subsidence no bacilli found very slight temporary lesions appeared elsewhere

Fig 3 —Marked general tuberculoid reaction

Fig 4 —Same patient about a year later Subsidence was complete and permanent (Eighteen years' observation)



Fig 1



Fig 2



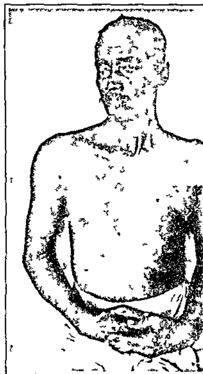


PLATE XVIII



Fig 1



Fig 2



Fig 3



Fig 4

trunks There is as a rule no constitutional disturbance except in cases with secondary infection or with reaction (*vide infra*)

Of all the symptoms described above there are only two which are diagnostic of leprosy namely definite thickening of nerves and impairment of cutaneous sensation (*see* Diagnosis)

There remain to be discussed certain matters common to cases of the neural type in general

Nerve abscess—One curious feature of leprosy of the neural type seen in India and particularly in Bengal is the not infrequent occurrence of oval or circular swellings on leprous nerves The swellings may occur in cutaneous nerves when they are usually small (the size of a pea) or in nerve trunks when they may be much larger The swellings are cold abscesses which may burst into the surrounding tissues and may discharge

sometimes in large numbers or previously undetected lesions may be rendered easily detectable At the beginning of the reactionary phase there is often an increase in the number of bacilli detectable in smears taken from the lesions and previously negative lesions may become positive

The condition of reaction in neural cases is always a temporary one and it subsides spontaneously sometimes in a few weeks or months but the reaction may cause severe damage to the nerves with permanent disability and deformity Reaction of the variety described in cases of the neural type although its appearance may be alarming is often not a bad prognostic sign since it is frequently followed by long periods of inactivity of the disease and it may be followed by permanent arrest of the disease In a few cases however reaction may recur even several times and at short intervals [illegible]

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in th [illegible]

In some cases the number and the size of the lesions may show little or no increase over long periods while in other cases the size and number of the

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PLATE XVIII—LEPROSY LEPROMATOUS TYPE

F[illegible] 1—S[illegible] Skin slightly

[illegible] n on face and

[illegible] ypop on Note

patches may increase steadily, and the number of nerves involved and the degree of involvement may also increase This increase in the size and the number of lesions may be extremely gradual, or, in cases with reaction it may be sudden and marked In some cases, the extent and degree of skin involvement may show little or no increase while the extent and degree of involvement of the nerves and nerve trunks supplying the affected areas may increase markedly, with resulting deformities trophic lesions etc

There are some cases of the neural type which tend to develop into cases of the lepromatous type, but recent studies have shown that this change from neural to lepromatous type is relatively rare, and is largely confined to neural cases of the 'simple' variety

The course of the disease in cases of the neural type varies markedly with the sub type

(i) *The course in neural cases of 'simple sub type*—Such cases do not often remain indefinitely of this sub type a few lesions of this type may subside spontaneously Some become lepromatous and follow a corresponding course as described later Most of the others become tuberculoid usually minor tuberculoid and follow a corresponding course

(ii) *The course in neural cases of minor tuberculoid sub type*—Minor tuberculoid cases are often characterized by extreme chronicity There are some cases in which lesions remain localized and subside within a relatively short time but in many cases the slight indolent activity goes on for years with extension of the lesions of the margin and healing at the centre with from time to time the development of new lesions and also a tendency for increasing involvement of

Minor tuberculoid cases may remain mildly active for many years sometimes up to thirty years or more In such cases apparent arrest even of long standing may be followed by renewed activity

(iii) *The course of tuberculoid and major tuberculoid cases*—In such cases the skin lesions are clinically more marked and the degree of nerve involvement is also greater as also is the tendency to tuberculoid reaction with positive bacteriological findings but nevertheless the periods of activity of the lesions are often very much shorter and may be limited to a few months or a year or two while the tendency to extreme chronicity is much less marked

In some ... lesions may appear suddenly and spread for a short ... will occur and the disease will ... periods and often permanently ... tuberculoid reaction with numerous bacilli in the lesions, may ... and completely, and the more marked the degree of tuberculoid activity the greater is this tendency to subsidence

Subsidence of marked tuberculoid activity is occasionally followed by minor tuberculoid activity of long duration or after a considerable interval by short periods of recurrence of major tuberculoid activity This recurrence however is usually not repeated many times, and the disease commonly becomes quiescent and arrested These phases of tuberculoid activity however may cause severe damage to nerves with permanent deformity

(iv) *The signs of subsidence in neural cases*—The patches instead of being infi... raised become thinned and atrophic and signs of fibrosis in the for... eriod in affected nerves ... in and fibrotic As the whi... d this increase must not rest... be

LEPROMATOUS TYPE

... the definition of the two main types ... esion is seen in cases of the severer ... ich there is little or no resistance to ... d spreading in the tissues of the body

with little or no tissue reaction The lesions are more diffuse in nature and more widespread throughout the body than in the neural type of leprosy, for the skin, nerves, mucous membranes, lymphatic glands and internal organs frequently show invasion Clinically, however, the chief lesions are

1 Slight diffuse thickening sometimes with erythema the skin having a shiny appearance and giving a soft 'velvety' feeling on palpation
2 Macules or circumscribed areas of skin with pigmentary change, differing from the macules of the neural type by having a smoother surface and an indefinite margin by showing no sensory change or thickening of the cutaneous nerves and by the fact that many bacilli are found on bacteriological examination
3 Nodule formation in the skin or subcutaneous tissue the nodules varying markedly in size and sometimes being so small as to resemble papules
4 Ulcers caused by breaking down of nodules

the dorsal aspect of the hands

One of the manifestations of leprous infiltration of the skin is the loss of hair, which may be seen all over the body but is most commonly seen on

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anæsthesia of the limbs caused by leprous involvement of the peripheral nerve trunks
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(shown
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used by
ling

In the lepromatous type of leprosy, the **mucous membranes** are very frequently affected, the mucous membrane of the nose pharynx and larynx being infiltrated, and sometimes showing nodulation and ulceration Such lesions in the nose may cause destruction of the nasal septum and falling in of the nose, and in the larynx may cause hoarseness and dyspnœa Symptoms of leprous infiltration are also frequently seen in the eye (*see* plate XVIII, figure 4), in the form of chronic leprous irido-cyclitis and leprous infiltration of the cornea Leprous invasion of the testes is also

Reaction in lepromatous cases—Reaction in the neural cases has already been discussed A condition somewhat similar is also seen in cases of the lepromatous type, but *in such cases the allergic nature of the reaction* is much less clear, the clinical manifestations of reaction are often very different, and the prognostic significance of the reaction is also different

In lepromatous cases, the manifestations of the reaction often include thickening, erythema, and sometimes ulceration of the infiltrations and nodulations in the skin and mucous membranes, the appearance of new nodules and infiltrations, sometimes very numerous and extensive, in the skin and subcutaneous tissues, and increase in the symptoms caused by leprous involvement of the mucous membranes, particularly of the nose and of the larynx ... kage of nose, or dyspnœa caused by ... sub acute leprous irido-cyclitis Thes ... ntly accompanied by constitutional disturbance, fever, rigors, prostration, etc

Reaction in lepromatous cases may be very severe, and not infrequently lasts for a considerable time, weeks, or months, and when it finally does subside, the patient's condition is often worse than it was before the reaction Also the reaction is apt to recur periodically, with a progressive deterioration in the patient's condition Such reaction, however, even if very severe, rarely causes death, though death from intercurrent disease during or after the reaction is not uncommon The importance of recog-

... cases ... 1 with ... *cases* ... osides, ... esions

become more marked and more widespread, and, finally, generalized

This process may be relatively rapid, taking only a few months, or it may be much slower and take several years The process of generalization may ... he occurrence of reaction, and, ... reactions may occur repeatedly ... on of the patient may rapidly deteriorate In such cases, death from intercurrent disease and weakness is not uncommon, and the whole course of the disease may be only a few years Even in such cases, however, if the patient can be tided over the period ... the disease may ... panied by mark

begins ma ... ty years the diseas ... oled and or more, deformed

Thus two ... acute and rap ... two extremes ... serious and may shorten life considerably, but subsidence with a greater or less degree of *deformity* and disability is not uncommon, and the prognosis of lepromatous cases, though grave, is not so hopeless as is sometimes stated

in the nerves, and the fibrosis of nerves is frequently accompanied by actual increase in the trophic changes, which should not be taken as indicating activity of the disease itself

CASES OF DOUBTFUL CLASSIFICATION

of both

There may, for example, be infiltrated patches with anæsthesia and some nerve involvement, but the patches may be smooth, have an indefinite margin and show numerous bacilli in smears Less commonly some of the lesions may be localized and appear to be neural, while other lesions may be

months the case may become more typical either neural or lepromatous,
ogical findings and prognosis
of cases in which clinical and other
ars, and accurate classification and

THE DISEASE IN GENERAL

The relation between the two main types —The idea that the neural

may react to leprous infection Those persons in whom there is some degree of immunity usually show the neural form while those in whom there is little or no immunity show a much greater tendency to develop the lepromatous form

It is true that there are some cases of leprosy which are not characteristic of either of these two main types, and which show some features of both, but these cases are, as a rule, not numerous It is also true that there are

some cases of leprosy of the neural type which later develop into cases of lepromatous type, but it is believed that these are not numerous and that they mostly belong to the sub-variety of the neural type which has been called '*simple*' The classification of cases of leprosy is not merely of academic interest, since it has important bearings on prognosis and treatment, and also on preventive work, since the lepromatous cases are the infectious cases

[illegible]

TABLE XIII

Findings	*Neuro-macular*			Lepromatous
	Simple	Tuberculoid	Tuberculoid major	
Clinical	Patches flat and smooth Nerve thickening, slight anæsthesia sometimes not marked	Margins of patch show thickening roughness often *papillation* Anæsthesia definite Nerves often moderately thick	Thickening of patch marked and not *confined to margin* Anæsthesia marked Nerve thickening often marked	Skin lesions smooth ill-defined, usually infiltrated, *may be nodular* Mucous membranes etc., affected Anæsthesia often found *in limbs but not* in skin lesions
Bacteriological	Usually negative	Rarely positive	Usually negative may be positive in 'reaction'	Always positive
Lepromin test	Negative or weak positive	Rarely negative usually weak or moderately positive	Practically always positive usually moderate or strong positive	Nearly always *negative*
Histopathology	Cellular infiltration not 'tuberculoid'	[illegible]	[illegible]	Foamy cell leproma No *tuberculoid* structure
Prognosis and course	Doubtful May become lepromatous, may become *tuberculoid* or may subside	[illegible] Rarely becomes lepromatous subsidence fairly common	[illegible] becomes lepromatous	[illegible] more often late after long period of activity Relapse common

Reaction —There are certain points which have already been mentioned but of which further discussion is advisable The first is the occurrence, in both of the main types of leprosy, of the acute or sub acute condition which has been called 'reaction' The failure to recognize this

condition and the fact that it usually subsides sometimes in a relatively short time even without any special treatment has been a frequent cause

a trophic nature caused frequently by trauma in tissues the vitality of which has been impaired by the destruction of the nerve supply including

deep (*see* plate XVIII figure 4)

DIAGNOSIS

say that even if a case appears exactly like one of leprosy unless one of these three signs is definitely present the diagnosis of leprosy should not be made

partial and not complete and may be very definite in some lesions and only very slight in other lesions The most useful way to test for loss of sensation is to test the sensation of light touch The patient's eyes are shut or bandaged the skin is touched with a piece of paper or a feather and the patient is asked to indicate with a finger the place touched Failure to respond indicates impairment Sometimes particularly in patches on the face touch sensation is retained

while the sensations of pain and of heat and cold are lost The sensation of pain may be tested by means of pin pricks in the suspected area and in normal skin the patient being asked to say which he feels most In doubtful cases the heat and cold sensation may be tested

Patience and care are necessary in testing sensation and allowance must sometimes be made for the patient's mental condition which may be dull It should also be remembered that the skin sensation is normally dull in certain parts of the body for example over the elbows and in areas of hard thick skin

The detection of nerve thickening—Here a word of warning is necessary A nerve is not thick merely because it can be felt Many normal nerves (*e g* the ulnar, posterior tibial, peroneal and sometimes the great auricular) are palpable and give pain on pressure A nerve should only be stated to be thick when it is definitely more thick than the same nerve on the other side of the body or, if both sides are affected, thicker than the same nerve in a person of similar build Examination for thickened nerves should include palpation of the ulnar above the elbow, the great auricular, the peroneal, and superficial peroneal nerves, and also palpation of the subcutaneous tissue around and proximal to macules, for thickened cutaneous nerves

The demonstration of acid fast bacilli—As has been stated above this is not often necessary for diagnosis but more often for judging whether a patient is infectious or not

Sites of examination—There is a common idea that the best way to demonstrate b asal mucous membrane This is not s the skin Nasal examination may be it is highly infectious or not but it stead of examination of the skin

Bacilli are rarely found in anæsthetic areas or in macules of the neural type though there may be a few found in the erythematous margins of such macules Bacilli are found in the lesions which have been described above as lepromatous *i e* areas of slight diffuse infiltration thickening nodule formation etc In cases of frequently found in the skin of the lobe of the clearly visible lesions

st generally useful method of examining the Take up a fold of the suspected skin between the thumb and forefinger of the left hand maintaining pressure to prevent bleeding and with a sharp scalpel held in the right hand make a slit vertically downwards into the corium Still maintaining the finger pressure with the point of the scalpel scrape the bottom and sides of the slit collecting material on the point of the scalpel Tissue cells not blood are required If there is excess of bleeding wipe away the blood before scraping Make a smear of the scraping on a slide fix by heat stain and examine

In nasal examination inspect the nasal septum for lesions take a suitable instrument and scrape away cells not blood or mucus from the lesion if visible or from the septum near the anterior end of the inferior turbinate bone make a smear on a slide fix and stain

It is most important that the slides and instruments used in making bacteriological examinations should be clean and free from acid fast bacilli This means that old slides should be used only after very thorough cleansing and that instruments must be very thoroughly cleaned and sterilized between each examination

Staining and examination of smears—The method of staining used is that of Ziehl Neelsen which is described in many textbooks The most important thing is that the stain shall be properly made the basic fuchsin being ground in a

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only one or two bacilli are found in a whole smear, it is advisable to repeat the examination in order to verify the finding

Cases with no cardinal signs —It has been stated that, if none of the three cardinal signs is found, a diagnosis is very rarely justifiable The most important exception is met in cases of leprosy in children In young children who have been in close contact with an infectious case, one often finds on the face, body, buttocks or limbs, depigmented patches in which there are no sensory changes, no bacilli, and no thickening of nerves In such c
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ful clinical examination and, in some cases, bacteriological examination are needed

DIFFERENTIAL DIAGNOSIS

Three groups of diseases may be mistaken for leprosy
skin which may resemble
vs Secondary and tertiary
tions of the skin (dermal
ns, lichen planus, erythema
Confusion may also occur
immatory conditions of the
skin such as erysipelas and cellulitis Tertiary syphilide may closely resemble a macule of the neural type of leprosy Dermal leishmaniasis (a post-kala-azar condition found commonly in Bengal Bihar, Assam and Madras) often produces depigmented patches, infiltrations and nodules, which very closely resemble those of leprosy Psoriasis with marked scaling of the lesions may produce an apparent but not real loss of skin sensation Leucoderma produces marked depigmentation with no loss of sensation The absence of the three cardinal signs of leprosy mentioned above distinguishes all these conditions from leprosy

Diseases causing loss of cutaneous sensibility —Many diseases of the central nervous system or of the peripheral nerves may cause some loss of skin sensation Neuritis may be caused by toxins or by vitamin deficiency Bernhardt's disease (neuritis of the lateral femoral cutaneous nerve), leac
traumatic i
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produced by interference with the blood supply in conditions such as Raynaud's disease and obliterative endarteritis

Most of these conditions are rare, some of them very rare In countries in which leprosy is common, a case of leprosy is frequently wrongly

the hands and feet, sometimes seen in Raynaud's disease and obliterative endarteritis, the deformities of tertiary yaws, deformities produced by trauma to nerves, involvement of nerves in callus formation after fractures, etc

Multiple infections —One point should be mentioned in conclusion
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and leprosy and dermal leishmaniasis

PROGNOSIS

The course of leprosy in its various clinical forms has already been discussed, and it has been seen how greatly this course varies The statement sometimes made that leprosy is always or almost always progressive and sooner or later fatal is therefore seen to be extremely misleading, *especially in view of the fact that in most countries where leprosy is* common, the neural cases form at least 50 per cent of the cases seen, while in some highly endemic countries such as India and Africa, the proportion of neural cases may vary between 70 and 90 per cent or more, and a high proportion of these is commonly of the tuberculoid sub type

It appears desirable to outline what is meant by a good or a bad prognosis in a disease such as leprosy Leprosy does not affect the vital organs and, in the absence of secondary infection, rarely causes death Therefore the prognosis is concerned largely with the likely duration and ... A good prognosis in leprosy
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nger time,
probably for many years, that during this time there is a possibility, or in *highly susceptible persons a probability, of death from weakness or* ... disease and that if and when the disease does finally subside,
marked disability and deformity
ctors to be considered are the type and sub-type of the disease and the race of the person affected These two factors are often inter-related since in certain races the lepromatous type ... the neural type predominates
prognosis is, on the whole, good, but
e lesions has a bearing on prognosis
variety in its more marked forms, the
prognosis is usually *excellent*, whereas the presence of the kind of lesion which has been called 'simple' indicates an uncertain prognosis, since in such cases the disease not infrequently develops later into the lepromatous *form*

In the lepromatous type of leprosy the prognosis is definitely poor

As already stated the race of the affected person markedly influences prognosis Many people of Indian and African races show leprosy in a mild and non-progressive form In Europeans, and in persons of mixed ... and other descent the disease is much more often severe and

The lepromin test, if positive, is a definite indication of a relatively good prognosis

Another factor possibly influencing prognosis is the age at which the disease appears, since children and young people often show relatively little resistance to leprosy, but even in children the definitely tuberculoid lesions have a good prognosis

The general physical condition of the affected patients and the presence or absence of intercurrent disease have frequently been quoted as having an important bearing on prognosis, but it is believed that their importance can easily be exaggerated

TREATMENT

Introduction —From ancient times until recently, leprosy has been regarded as a disease for which treatment was of very limited value

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are

leprosy of the neural type, with deformities, ulceration etc, obtain little or no benefit from treatment The severe or advanced cases of lepromatous type are frequently difficult or impossible to treat, because of frequent

The elimination of
aria, and amœbiasis,
ular hours, sufficient
tance
term 'special'
believed that
e that quinine
r kala-azar or

Historical—The use of the chaulmoogra group of oils in the treatment of leprosy apparently originated in India at least 2,500 years ago for it is described

in the *Sushruta Samhita* of about that period It has recently been pointed out

many centuries ago

In the nineteenth century, European physicians in India found this oil being *used by practitioners* of Indian medicine, and began to take an interest in it The oil was administered by the mouth and by inunction and various workers in India and other countries tried this form of treatment some reporting some benefit, and others little or none From 1879 onwards various chemists studied the chaulmoogra oils, isolated their fatty acids and prepared their salts and these

The ethyl esters of
1907
394 in Egypt where
ted various forms of
ids The use of these
The excellent results
orkers particularly in Hawaii and in India encouraged
reatment in most countries of the world,
widely recognized it is now the standard

s in common use are hydnocarpus oil
elmintica etc) with 4 per cent creosote,

e
f
reduced by warming the oil to body
must be obtained from a reliable source

Dosage—For
recommended Beg
5 or 6 c cm given
larger doses in certain suitable cases and doses of 20 c cm a week or
a local reaction or pain, the doses
on occurs,
then only

ably given
cutaneous
injections

Intra-muscular injections should be given deep into the upper part of the gluteus maximus muscle Thorough massage of the part after injection assists rapid absorption Subcutaneous injections are best given into the loose subcutaneous tissues *of the fleshy parts of the limbs By nearly with-*
up to 3 or

sions them-
e needle is
and about

should subside in
a second time until a month has elapsed

If all the lesions have recently been intra-dermally injected, the other two methods *should* be used Usually not more than two or three cubic centimetres are given *by intra-dermal injection* at one time, the remainder (if any) of the dose ordered being given by other methods

The intra-dermal method is suitable for injections into the macules of the neural type and into the lesions of the lepromatous type. Good results have also been reported with injections given near and around the affected nerve trunks and into the skin and subcutaneous tissue in their distribution

Duration of treatment and assessing results—The duration of treat-

In slight cases of
in a few weeks or
be prolonged and
prolonged There

to relapse may at once be detected and treatment resumed

In assessing results of treatment, accurate records of clinical and

id attri-
ases, if
lesions
ay dis-
appear, the anæsthesia may become less extensive, and the bacilli, if

Other forms of special treatment.—As already stated, hundreds of remedies have at one time or another been used and advocated in the treatment of leprosy and every year sees additions to this number The common sequence of events is as follows Some worker tries a new remedy

have been used

Numerous workers have used injections of preparations of heavy metals, particularly

the disease in
general and also in
such as eye
affections but other

Potassium iodi

idual increase
from small to large doses has been used by various workers during the last sixty years
other
agreed
specifi
is a
resolu
Cairo, 1938, on
this matter reads as follows —

'With regard to treatment with potassium iodide the use of this drug is frequently followed by disastrous results It is therefore to be discouraged for the purposes of diagnosis treatment, or as a test of recovery unless in very skilled and experienced hands'

Various workers have used *vaccines* consisting of supposed cultures of lepra bacilli, or else *sera produced by* 'immunizing' animals with these vaccines, or with material obtained from leprous patients Examples of these preparations are Rost's 'leprolin' and Reinsteirna's serum The results of such treatment are not [illegible]

Ever since their [illegible]

used in the treatmen [illegible]

the leprous lesions after intravenous injections, and lesions may break down, ulcerate and then heal after large doses, but permanent improvement is usually not seen

Various workers have reported beneficial results from the administration of preparations containing large amounts of one or more of the different *vitamins* Reports of this form of treatment are very contradictory, and their value has not been proved

One of the latest new treatments for leprosy has been the injection of *diphtheria-formol-toxoid* The strikingly beneficial results originally reported have been confirmed by no one, and some workers find the treatment definitely harmful

The induction of a high temperature either in the lesions themselves or in the patient's body as a whole has been used by various workers, and various methods of *heat therapy* have been employed, but the results are not striking or consistent

Local treatment of lesions —In addition to the local treatment discussed later under 'Management of complications', various forms of local treatment of the lesions themselves may be used

All workers are agreed on the value of local irritation to lesions of all types and some of the benefit produced by injection of hydnocarpus preparations may be caused by this local irritation Various other forms of irritant have been used, such as carbon dioxide snow, but a very useful and more widely practicable measure is the application to the lesions of trichloracetic acid Solutions of the crystals in water of varying strengths from 1 in 1 to 1 in 4 (by weight) are used The stronger solutions are used for touching nodules and other small but prominent lesions, the weaker solutions are used for application to larger areas of skin, infiltrations, patches, etc The solution is applied with a small cotton-wool swab held in forceps, and the application should be followed by whitening of the skin and desquamation, but not by ulceration A little experience is necessary in judging how much solution to apply and in what strength, and care is needed to avoid burning the skin, with the production of scars and sometimes keloids

Another form of local treatment is the surgical removal of suitable lesions suitably situated If the only lesion of leprosy is a single small patch, surgical excision may be practised, and is usually not followed by recurrence if the original lesion is of the tuberculoid sub-type Sometimes more than one such patch may be excised [illegible]

[illegible]

allowance must be made for contraction produced by fibrosis when the incision heals

times a day with a bland fluid such as normal saline or with mild anti septics and local applications of mild caustics or stronger antiseptics can then be made to the actual ulcers present in the nasal septum In this way such ulcers will frequently be made to heal the discharge of the lepra bacilli from the nasal mucous membrane can be much diminished or pre vented and the patient thus rendered much less infectious

MANAGEMENT OF COMPLICATIONS

Reaction —In the milder forms of reaction particularly the tuberculoid reaction seen in neural cases hospitalization may not be needed and the reaction will subside in time without any treatment beyond the cessation of the administration of hydnocarpus preparations or any other medicament which may have precipitated the reaction Concomitant diseases present such as malaria should be treated

In the more severe forms of reaction particularly in lepromatous cases hospitalization is necessary for proper treatment

The patient should be kept in bed properly nursed and given suitable general treatment diet aperients etc Various forms of medicinal treatment of reaction have been recommended such as the injection of small doses of antimony in the forms of potassium antimony tartrate given intravenously or of [illegible]
of large amounts of
forms of treatment
affections severe ne
as described later

In time the fever and the other symptoms will subside and hydnocarpus treatment when resumed must be undertaken with great caution as to dosage

Trophic lesions —By care it is frequently possible to minimize if not prevent the development of trophic lesions in cases of leprosy The lesions are the result of the damage to nerves chiefly those supplying the feet and hands Careful examination of patients may reveal marked infiltration of the ulnar or median nerves of the peroneal or tibial nerves and suitable treatment for this neuritis (*vide infra*) may minimize the nerve damage and the res[illegible]

[illegible]

extension of the fingers may also be of value

If the nerves supplying the hands and feet are seriously affected steps should be [illegible]
from hea
allowed
Similarly
specially made it necessary or adapted to prevent pressure on points where trophic ulcers are likely to develop such as the head of the first metatarsal or the os calcis

[illegible]

The trophic ulcers of the foot are of two types, firstly the simple trophic ulcer *of the sole without necrosis of bone*, secondly, the trophic ulcer with necrosis of the underlying bone In practice it is found that most trophic ulcers are of the second type

In the absence of necrosis of the bone, the ulcer will usually heal if the patient is kept off his feet and suitable local applications are used *It is most important to prevent pressure of injury to the feet*, by keeping the patient in bed or allowing him to walk only with the use of crutches, until the ulcer has finally healed The ulcer should be kept dry and clean, and all thickened dead skin around it should be kept pared off, and the ulcer encouraged to heal from the bottom Many different local applica-

to be of outstanding value

id other chlorine antiseptics,

be used for cleaning septic

ulcers, but prolonged soaking in antiseptics is to be avoided Antiseptic or bacteriostatic powders such as sulphanilamide may be used, and the ulcer *may be sealed with elastoplast or plaster of paris, and the dressing changed* at long intervals

If bone necrosis is present the ulcer may heal temporarily, but not permanently unless the bone is removed or else discharges itself through the ulcer The bone necrosis can usually be detected by the use of a probe

examination

The dead bone should be removed by operation, which should be carefully performed to avoid all damage to surrounding healthy tissue Local anæsthesia is induced by infiltrations round all the nerves at the ankle Incisions should always be made on the side or dorsum of the foot and not on the sole In order to minimize deformity, only dead tissue should be removed Since some secondary infection is usually present, it is inadvisable to close the incision by sutures

Secondary infection of trophic lesions, often of a virulent nature, is not uncommonly seen, and, in the absence of proper surgical treatment is one of the commonest causes of death in cases of leprosy It commonly leads

gangrene of the affected part The virulent

h a perforating ulcer, but also without

as the result of blood-borne infection

In the past, early and radical surgical treatment of these acute septic conditions has been practised in the form of amputation of digits, hand, foot, or limb, and has given excellent results, without such operations patients frequently die Although nothing has yet been published *it appears that*

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such operations as

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n some patients, how-

ye affections are very

or sub-acute leprous

The patient should

be kept in a darkened room or wear an eye shade the pupil should be

etc

Severe neuritis—This may be seen either during a reaction or apart from it and is most common in the ulnar nerve Palliative treatment includes such procedures as the injection of cobra venom to relieve the pain local application of heat etc in the form of hot compresses or of diathermy Subsidence is frequently seen following the operation for *removal of the nerve sheath* around the affected part of the nerve which is frequently a limited portion of the ulnar nerve above the elbow Such operations may also minimize subsequent deformity

Respiratory obstruction—Obstruction of the larynx may be caused either by the presence of marked lepromatous lesions, especially during the phase of reaction in which case it is acute or sub acute or by the fibrosis which follows the healing of such lesions in which case it comes on very gradually In either case **tracheotomy** is sometimes needed for the relief of this condition which may otherwise cause death When the reaction has subsided it may be possible to remove the tracheotomy tube but the advisability of removal is doubtful for subsequent reactions may necessitate replacement In cases caused by fibrosis the tube has to be kept in permanently

THE CONTROL OF LEPROSY

tion of careful and thorough treatment of cases of leprosy no control measures are likely to be effective for the co operation of those suffering from leprosy will not be secured nor the sympathy and support of the public

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Incisions sl ot

on the sole be

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to close the incision by sutures

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In the of these acute septic conditions has been practised in the form of amputation of digits, hand,

such operations patients

blished, it appears that

markedly influenced the

ssity for surgical treat-

le

by such operations as

pointing results

the preventive measures

already outlined should be adopted to p rence

Leprous eye affections —In the lepromatous type of leprosy, slight attract little attention

In some patients, how-

eye affections are very

or sub-acute leprous

The patient should

be kept in a darkened room or wear an eye shade the pupil should be kept constantly and fully dilated with atropine and hot boric fomentations

etc

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THE CONTROL OF LEPROSY

The control of leprosy should be based on knowledge of the epidemiology of the disease which has already been outlined

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public

In various countries where leprosy is found, the following measures [illegible]

[illegible] for the application of such measures is usually made

Where the number of persons with leprosy is not unduly great, and where reasonable financial resources are available, the control of leprosy is usually [illegible] of infectio[illegible] in favour[illegible]

In many countries where leprosy is common, however, the large number of cases, the lack of financial resources, the lack of trained workers and [illegible] e rendered it [illegible] st leprosy on [illegible] lines but on a voluntary basis

Modifications of the older type of isolation measure have rendered [illegible]

great importance is the establishment of efficient treatment in the isolation institutions, with the discharge of a considerable number of patients on becoming non-infectious In a few centres, arrangements have been made for men and women with leprosy to marry and live in leprosy institutions, usually of the colony type, under proper safeguards to prevent the infection o[illegible], either children born may [illegible] the Philippine Islands, or [illegible] been sterilized as in Ja[illegible] adopt leprous children

In some countries where leprosy is common, the giving of alms to leprous beggars is widely practised as a religious duty, and large numbers are thereby encouraged to gain a living by wandering around the country begging A considerable number of these beggars are infectious cases, and, while it is true that their contact with the healthy population is limited, the menace to public health cannot be ignored Special institutions or separate sections of leprosy institutions may be needed to deal with [illegible] persons demands measures [illegible] e general population

[illegible] *Preliminary measures*— [illegible] any area or country, the [illegible] suitable workers with the necessary knowledge and training in leprosy work to make a preliminary study of the problem If trained workers are not available, suitable men are appointed and delegated for training at a suitable centre, and if necessary sent abroad for this purpose

2 The carrying out by this trained staff of a general survey of the extent, the nature, and the severity of the leprosy problem in the area to be dealt with

3 The framing of a leprosy control scheme to be based on the general lines outlined below, and the framing of suitable legislative support for the scheme

(a) Leprosy surveys —In addition to the general preliminary survey

in
ing
ral
on-
elf-
support

(d) Provision for home isolation of infectious cases —The main point

lated patient
outside the
o not involve
e isolation if
the isolation
nt for main-
course
untries,
ferable
ts of a
village, suitable buildings, and arrangements for feeding and maintenance are required

(e) Provision of social services —These services are needed to aid patients themselves and the dependants of patients, particularly of isolated patients, who may be left unprovided for Small grants for the maintenance of patients or
the supervisic
activity of su
healthy child
securing of employment for such persons

(*f*) Provision of institutional *accommodation for disabled* non infectious cases —A considerable number of persons of this type ar usually *found* They are non-infectious, but because of the presence o deformities of hands and feet, trophic ulcers, etc, they are permanently

and such facilities should be provided

(*g*) The organization of suitable propaganda to create the publi opinion necessary for the success of the measures.—*This matter is of vita* importanc

(*h*) … orough training of th medical s … and practical instruction should be included in the ordinary pre-graduate medical curriculum, but centres of thorough post-graduate training are also needed

can play in such work, etc,

d, but it is certainly advisable that the

and their dependants

In many countries where leprosy is common, the inauguration of a complete scheme of leprosy control along the above lines is impracticable, and in such circumstances an attempt should be made to concentrate on certain parts of the work which are of the greatest importance It may *for example* be impossible to isolate all the infectious cases, and in such circumstances it is best to concentrate on preventing contact between infectious cases and children and young people Infectious persons living in

surveys,

indication of the effectiveness or otherwise of measures adopted may be obtained by a demonstration of the presence or absence of a fall in the incidence of *leprosy* in children on periodical examination of all school children in the areas In some countries, the reduction in the incidence of leprosy has been demonstrated by the fall in the incidence in young men *reporting for compulsory* military service

The results of compulsory isolation measures have varied markedly In some countries, for example Norway, where the serious leprosy problem of sixty years ago has almost entirely disappeared and where public opinion gave strong support to the measures the results appear to have been excellent In some other countries, particularly where public opinion has not given the necessary support the laws have been evaded and the measures have met with little success In some countries, Japan and the Philippine Islands for example, a moderate degree of success appears to have been attained, but the work has not yet continued for sufficiently long to make possible a final judgment of its effectiveness In Brazil a comprehensive scheme of leprosy control has recently been inaugurated, but it is too early to judge its results

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YAWS AND ASSOCIATED DISEASES

PINTA

BEJEL

Introduction—There are at least three tropical syndromes that have been given the status of named diseases which are caused by spirochætes morphologically indistinguishable from the parasite of syphilis they are yaws pinta and bejel All three are looked upon as modified forms of syphilis by some workers and as distinct diseases by others They have many common features but perhaps the most important is that they are all three non venereal in origin

There are probably other allied similar or identical diseases in other primitive and isolated populations An example of such a condition is *Irkintja of Central Australia recently described by Hackett (1936) who* believes that the condition is identical with or at least closely related to yaws In this condition there are early lesions similar to those of yaws usually in childhood and later gangosa boomerang leg and keloid scarring

YAWS OR FRAMBŒSIA

Definition—Yaws or frambœsia (French *framboise* = raspberry) known as *pian* in the French colonies and by many other local names elsewhere is a contagious disease resembling syphilis but non venereal in origin occurring mainly amongst aboriginal populations in the tropics

characterized in its florid stage by multiple granulomatous lesions of the skin and later by a variety of lesions of the skin subcutaneous tissues and bones it is caused by a spirochætal organism *Treponema pertenue* that is readily recoverable from the cutaneous lesions

Historical—It is not possible to identify definitely as yaws any of the skin diseases that are mentioned in ancient writings tho gh several wo ld pass as this disease

century

EPIDEMIOLOGY

Geographical distribution—It has a wide tropical distribution and all the more important endemic centres are within the true tropics It occurs in Central and South America in the West Indies extensively in equatorial Africa including the Sudan and Abyssinia in India Burma Ceylon Indo China Malaya and the East Indies generally and in Northern and Central Australia and certain Pacific islands The most important sub trop cal endemic foci are in Algiers and Tripoli in North Africa in Assam in India and in northern Burma

In India it is much more widespread than is generally supposed occurring in Cochin Travancore Hyderabad the Central Province Chota Nagpur Bihar Santhal Parganas Chittagong Hill Tracts Manipur Cachar and several other places in Assam Nowhere however has it assumed serious epidemic proportions and spread to the general populations of the plains of India

countries where conditions are particularly suitable for its spread and die down or disappear when all susceptible persons (*i e* the children born since the last epidemic wave and the few adults who previously escaped infection) have been infected

Epidemiological features—It is a disease of rural districts rather than towns The incidence of the disease varies considerably In certain isolated islands and other primitive populations practically every individual becomes infected sooner or later and usually sooner that is in childhood In some tropical countries in equatorial Africa for example the disease is a very serious public health problem (*e g* over 300 000 persons were treated within a few years in the Belgian Congo which has a population of ... 10 000 000

of cases treated annually will amount to only a few hundred at a generous estimate

The tropical distribution suggests that temperature is an important factor Experience has shown that when a case is imported into a temperate country the infection does not spread It has been found in India that the hill folk who tend to get the disease when they come down to the foot-

hills or into the hot, humid plains, do not take the disease back to their own villages if these are situated at any great height

Humidity is also important, and most of the endemic countries enjoy a high degree of humidity for a considerable part of the year, and luxuriant vegetation, however, the disease also occurs in Algeria and Tripoli which are relatively dry countries, as well as being outside the tropics

Racial distribution—In its natural form, it is a disease that is confined almost entirely to primitive peoples This is most strikingly demonstrated in India, where it occurs amongst primitive hill folk, but seldom spreads to any extent amongst the plains' population (*vide supra*) This is almost certainly not due to personal susceptibility or immunity, as the disease is easily transmitted experimentally to individuals of any racial type but probably to the habits of the people who have a low standard of personal cleanliness, and live and sleep in primitive huts closely huddled together

[illegible]
to th [illegible]
but a [illegible]
it, mothers frequently contracting the infection from their children In highly endemic areas, children usually contribute at least 90 per cent of the cases but in isolated communities where the infection is reintroduced at longer intervals a large proportion of adults will become infected All contagious infections tend to spread more rapidly amongst children on *account of their habits, but the most important influence in these cases* is undoubtedly the immunity acquired by adults during previous outbreaks

Most writers report that males are more commonly infected than *females This is probably due to the greater freedom allowed male children* Chambers (1938) points out that in Jamaica the only age groups in which females predominate is from 20 to 29 years, this is an age at which women would be closely associated with infants and children and would be likely to be infected from them

ÆTIOLOGY

Historical—Castellani in 1905 first isolated from yaws lesions an organism indistinguishable from the organism of syphilis, and named it *Spirochæta pertenue*, both these organisms were later placed in the genus *Treponema*

The causal organism—*Treponema pertenue* is a very slender (0 25 microns) spirachætal organism, from 8 to 18 microns in length, it has from five to a [illegible]
1 micron [illegible]
flagellum [illegible]
morphologically identical with *Treponema pallidum* the causal organism of syphilis

Culture and animal inoculation—Culture of this organism was claimed by Noguchi and later by Hata, the former grew it in ascitic fluid to which kidney tissue had been added, anærobically Most other workers have failed to satisfy themselves that they have produced a true culture, and at any rate the procedure is not a practical diagnostic method

Successful inoculation has been produced in man higher apes monkeys, and rabbits, in the two latter animals only local lesions are produced

Distribution in the tissues —The spirochæte is found in the primary and secondary skin lesions in the spleen and in the bone marrow their presence in the blood has been demonstrated by inoculation

Transmission —This takes place by means of direct contact the organism from the exudate of a lesion entering the new host through an abrasion although possibly an invisible abrasion in his skin Whenever the point has been carefully investigated a history of close contact with some person with florid lesions has been obtained in almost every case and when mothers are infected by their infant the common sites of the primary lesion are on the breast at the bend of the elbow or on the hip places where direct contact most commonly occurs The mechanical transfer of infection by means of flies is

perimentally incriminated as a mechanical transmitter in Jamaica Certain species of *Musca* have also been shown to be potential mechanical carriers of viable spirochætes but a biological cycle in any insect has never been seriously suggested

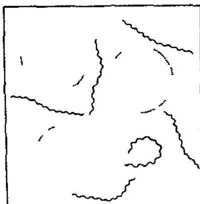


Figure 141 *Treponema pertenue*

Man is the only known reservoir of infection

Congenital transmission never occurs

The relation of the causal organism of yaws to that of syphilis —This is a problem on which much work has been done during the last four decades without any final conclusion yet being reached

Morphologically the organisms are identical culturally no definite differences have been established serologically in the antigenic structure of the organisms common elements but also distinct differences have been shown to exist in animals readily distinguishable lesions are produced by these two organisms and in man there are marked differences in the two diseases they cause

Whether syphilis is a specialized form of yaws that has in the course of years undergone some change through being transmitted venereally amongst people
that has lost
passage amongs
heavy malarial
they both arose
and each devel
demic interest
far greater thar
same organism
Treponema per

Immunology —Immunity to superinfection is not immediate and complete but it appears to take several months or even years to develop and

if early treatment is given reinfection becomes possible Many cases of syphilis have been reported in individuals who have or have had yaws and conversely yaws has developed in syphilitics but there appears to be little doubt that populations that have been heavily infected with yaws enjoy some degree of immunity from syphilis The reverse is probably true but not so easily demonstrated unless one takes the view that the relative immunity to yaws of towns folk in countries where yaws is common in the rural districts is due to the heavy syphilization of the town dwellers but this argument cannot be universally applied

An m — with syphilis gives complete
tion only gives partial pro-

The Wassermann and Kahn reactions become positive three to four weeks after the appearance of the primary lesions and are constantly positive after about the eighth week they remain positive for several years or as long as the infection is active Those affected with yaws in early childhood usually lose their positive serum reactions after puberty so that whenever positive results are obtained in such persons they may usually be taken as evidence of a superimposed syphilis infection

PATHOLOGY

The spirochæte gains entry through an abrasion or possibly even through the unbroken skin and enters the deeper layers of the epidermis where it multiplies producing a cellular (polymorphonuclear and plasma cell) reaction and œdema The proliferation of the cells of the malpighian layer causes both a downgrowth of the interpapillary processes and is also a general upward growth that pushes up and eventually splits the stratum corneum into lamellæ between which fibrinous coagula form There is also increased vascularity plasma cell and lymphocyte infiltration and some proliferation of the reticular cells of the papillæ The spirochætal infection is mainly confined to the epidermis but eventually spreads to the surrounding lymph channels in the dermis and finally reaches the blood when generalization of the infection occurs

From the moment of entry of the spirochæte the lesions of this first stage take three to four weeks to develop and after generalization has taken place there is usually an interval of two to three months before the secondary lesions appear these are multiple and appear on many parts of the body surface The typical secondary yaws lesion is similar to the primary lesion described above

After a much longer interval up to several years a third group of lesions may appear typically they are gummatous inflammatory lesions of the subcutaneous and other tissues that may lead to gummatous ulceration of the skin to fibrotic tumours in the skin or subcutaneous tissues especially around the joints to gumma and rarefaction of the bones and/or to diffuse keloid like formations of the skin

It is suggested that the tertiary lesions are of the nature of an allergic reaction

Some writers describe tertiary lesions of the viscera and the arteries similar to those of syphilis but the authenticity of such lesions seems doubtful and most observers agree that the lesions of yaws are mainly epiblastic that is to say affecting the skin and bones in contrast to syphilis

in which the causal organism is panblastotropic that is it affects the tissues of all three embryonic layers

The lesions that occur can thus be placed in three groups the primary or initial lesions (mother yaw) the secondary or lesions of the generalized stage and the tertiary lesions or sequelæ Between these three stages

SYMPTOMATOLOGY

The clinical picture corresponding to these three pathological stages will be considered under three separate headings —

The primary stage—There is usually a single lesion but it is possible for there to be more than one if infection occurs at two places After

e crater thus formed is filled with exudate which takes on the charac

when this crust is re

itous tumour will be

apidly filled by more

s coalesce forming a

single lesion an inch or even two inches in diameter There is usually an area of hyperæmia around the lesion and in dark skinned subjects there may be a halo of hypopigmentation around this The lymph nodes in the neighbourhood are often enlarged and slightly tender The primary lesion is sometimes pruritic and in other cases painful but usually it is both painless and non irritating

In some cases it is not possible to find any evidence of an initial lesion and in others a maculo papular or even a macular spot takes the place of the granulomatous initial lesion

This initial lesion may continue to develop and may still be active when the secondary lesions appear but it usually then tends to heal or on the other hand it may heal early so that there is only a scar to be seen when the second stage commences

This initial lesion is apparently not usually accompanied by any constitutional symptoms it is not however possible to be dogmatic on this point as the people who usually suffer from this disease are not very intelligent and would probably not notice or at least not report slight malaise

The site of the primary lesions will vary according to circumstances depending as they do on the one hand on abrasions and on the other on

lesions are very rare and are placed as low as 2 per cent in some populations

The Secondary Stage—The secondary lesions appear from six weeks to three months after the full development of the initial lesion The onset

of the secondary stage is often associated with mild constitutional sym toms, a low fever, *not often above 100° F*, joint pains, pains in the bon and general malaise

A large variety of secondary lesions are described, and in the textboo *these make a formidable array* that must alarm and confuse the studer However, the pathological processes that produce these lesions are, qual tatively at least, the same, although they may vary in number, in distrib tion, and in the extent to which *they progress before resolution, as well* being influenced by such variable factors, as, for example, individu and racial differences in skin texture

The individual foci may produce very minute papules with little ker tosis and, if these are arranged in groups, they will give the appearance **macules,** or, if they are slightly larger and very numerous, that of a lic **enous rash** When these lesions *resolve*, they desquamate, *producing* tl **furfuraceous desquamation** that is described If there is a little mo keratosis, a **papular** or **papulo-macular eruption** will result The majori of these papules will subside, but some will continue to develop and tl typical **papillomatous frambœside,** very similar to the initial lesion, wi appear These yaws papules sometimes develop in the form of a ring wit an area of unaffected skin in the centre, this particular form is given tl name *ringworm yaws*

Finally, when these lesions develop in the skin of the palms or sole on account of the great thickness of the epidermis there, the clinical result are very *different from those in other parts of the body* Many types o plantar and palmar yaws are described, and given various and ofte vernacular, names but amongst the commonest types are the vesicular c papular eruptions that lead to separation of the superficial layers of th

through ... and crippling nsive granu ng deformity

of the feet known as **clavus**

The lesions appear in crops, so that there will often be lesions in al stages of development present *at the same time* *This will also mean that* the order of development may not seem to be consecutive and, for example the furfuraceous rash may appear after a typical frambœside (from an earlier crop) has already developed

Thus, there are three types of secondary lesion, the early diffuse fram bœsides of several types, the typical papillomatous frambœside, and the late plantar or palmar lesions

Sites—The diffuse lesions that is, the papular eruption, the furfuraceous rash, etc, appear mainly on the trunk and the limbs whereas the typical frambœsides appear most commonly on the face, the limbs and the buttocks, also on the trunk, neck, *and perineum but the scalp is very sel*dom affected, the junction of skin and mucous membrane, (*e g*, around the anus the mouth, and the alæ nasi) are the most favoured sites

Progress.—The fully-developed typical papillomatous frambœsides vary from the size of a pea to that of a large walnut (3-4 cm), but they will usually be present at all stages of development and healing They may heal within a month or so, or persist for years When they heal, either spontaneously or as a result of treatment, they leave a white scar, this scar may become pigmented in the course of time or it may persist for life

The Tertiary Stage.—Most of the lesions in this stage owe their association with yaws to the fact that they are common lesions in populations

These lesions may appear at any time from one year to twenty years after the appearance of the secondary lesions Amongst the earliest and most typical tertiary lesions are **juxta-articular nodules.** These are hard, fibrotic swellings in the subcutaneous tissue around the joints, varying in size from a pea to a pigeon's egg They are usually attached to the ligamentous tissues of the joint or tendon sheaths, but the skin is freely moveable over them—at least at first Later, probably as the result of trauma, it may become fixed They are not normally painful but from their position (usually on the outer side of the joint), are very liable to damage The knees and ankles are the commonest joints affected, but the nodules may occur around almost any joint, and similar fibrotic swellings are sometimes found in the subcutaneous tissue in other parts of the body

Gummata develop in the subcutaneous tissues, and eventually ulcerate through the skin causing chronic septic ulcers

There are several types of bone lesion A soft painful swelling of the periosteum, particularly of the tibia and ulna that occurs relatively early in the disease is often classed as a secondary lesion There is also an

spontaneous fracture a common occurrence

There remain two clinical syndromes that are now recognized as being usually, although perhaps not always, sequelæ of yaws infection, namely gangosa and goundou The former usually occurs in adults who have suf-

fered from yaws in childhood, but the latter often appears at an earlier date and affects children The evidence for the ætiological connexion between these diseases and yaws ...

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logical factors

Gangosa, or Rhinopharyngitis Mutilans—This is a condition in which there is ulceration of the mucous membrane of the nasopharynx and nose, which involves and eventually destroys the soft tissues, cartilages, bones and eventually the skin, working from within outwards, until the whole mouth, nose, nasoph...

large fungating cavity with

ged by the remains of the

occur in which the process is halted, either spontaneously or as a result of treatment, before the destruction has been complete The condition was at one time associated with ...

hood

Somewhat similar conditions may be produced by rhinoscleroma and by espundia (*q v*)

Goundou.—In this condition, there is a bony exostosis of the nasal processes of the upper maxilla, usually bilateral It is usually associated with severe headaches, some nasal obstruction, and a sero-purulent and sometimes blood tinged discharge from the nose The skin over the exostosis is normal and freely movable The tumour may obstruct the lacrymal ducts and interfere with the line of vision, but does not encroach on the orbit or otherwise affect the sight

DIAGNOSIS

Clinical—The typical yaws lesion is so characteristic that it is unlikely to be mistaken for other conditions but many of the other less typical lesions may well be, and it will often only be possible to diagnose their nature clinically by their association with the typical framboeside

Laboratory—From the primary and from many of the secondary lesions, especially from the framboeside it is possible to recover the spirochæte without much difficulty

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by Tribon-

hese stains

(*see* p 242)

Differential diagnosis—Syphilis and leprosy are probably the two diseases with which yaws has been confused most frequently in the past, but the protean nature of the manifestations of yaws make it possible to confuse the individual lesions with those of almost any skin disease and of many ulcerative conditions, *e g*, pityriasis rosea, versicolor and pilaris, lichen planus, acne vulgaris, psoriasis, icthyosis, impetigo contagiosa, tinea, eczema of various forms, lupus erythematosis and vulgaris,

oriental sore and South American leishmaniasis ulcus tropicum, veldt sore, and septic varicose and malignant ulcers

The joint pains in the earlier stages and the juxta articular nodules ... the juxta ... other parts

TABLE XIV

The following table gives the main points of differentiation between yaws and syphilis —

	YAWS	SYPHILIS
Epidemiology	Primitive people Children under 14 years Seldom venereal Never congenital	Civilised people Adults Usually venereal May be congenital
Tropism	Epiblastotropic	Panblastotropic
Primary lesion	Extra-genital Variable but usually typical frambœside Glandular involvement—not constant *and glands soft* Wassermann & Kahn reactions—negative	Genital Typical indurated chancre Commonly shotty en*largement* Often positive
Secondary stage	Typical frambœside and furfuraceous desquamation Mucous membranes not affected Eyes unaffected Alopecia —unknown Constitutional symptoms —slight Wassermann & Kahn reactions —positive	Rash sore throat etc Often affected Iritis common other eye lesions may occur May occur May be marked Positive
Tertiary stage	Lesions superficial and obvious, troublesome and crippling non fatal Nervous and cardio-vascular systems —not affected (according to most authorities) Blood Wassermann reaction —usually positive but may be negative	Lesions mostly of viscera subtle often fatal Both affected Always positive
Para lesions	Do not occur (according to most authorities) C.S.F Wassermann reaction —never positive	Tabes and G.P.I may occur Often positive
Treatment	Does not respond to mercurial treatment	Will respond to mercurial treatment

PREVENTION

This disease is essentially one of uneducated populations amongst thes...

... is therefore the first principle in prevention This may however be too idealistic or at least too long term a policy for most circumstances and organized wholesale treatment of the population will in most circumstances be the best method to adopt. How

this treatment can be provided will depend entirely on the special circu stances Where the people are easily accessible, a system of perman hospitals and dispensaries, with doctors, *nurses, and health visitors*, can arranged, but for isolated communities it will be necessary to have itinera units that can move from centre to centre It has been shown that *though a full* course of injections may be necessary to ensure a compl cure (*vide infra*), by giving even one or two injections to each infect individual it is possible to reduce the disease *in a population very* co siderably, as well as to provide much relief to the infected individuals

It is unnecessary to discuss such obvious, but in the circumstanc totally impracticable, measures as isolation and early treatment of abr sions

TREATMENT

This can be considered under the four headings, (*a*) general, (*b*) loc (*c*) specific, and (*d*) subsidiary

a) **General treatment**—There is little that need be said about ge eral treatment, *it is obvious that a well-balanced* nourishing diet, suitab clothing that can be changed daily, warm baths, 'hot, demulcent drink regulation of bowels, and so forth, are ideal recommendations, but in t conditions under which yaws usually has to be treated it will be impossib to apply them and one will usually be quite satisfied if it is possible *give the specific treatment to all those that require it*

b) **Local Treatment**—More rapid healing will certainly be broug *about if the lesions are* bathed *in some* antiseptic lotions, the writer h used mercurial lotion and acriflavine, 1 in 1000, but probably some of t newer antiseptics will be more effective For applications that can be give to the patient most usefu These will hav id preventin the external s ibtful if the will have any

c) **Specific treatment**—The specifics are arsenic and bismuth Ther are three different lines of treatment which can be adopted according t the varying circumstances, or perhaps judiciously combined, namely (i) in travenous *or intramuscular* arsenicals, (ii) intramuscular, bismuth an (iii) oral arsenicals

(i) The most rapid and dramatic results can be obtained by neo arsphenamine (*e g* neosalvarsan) injections, in doses up to 0 90 gramme fo men, 0 60 g for weak or small men and for women, 0 30 g for a child unde 10 years, and *0 10 g for a child under two years, or, on a* weight basi 0 01 g (one centigramme) per kilogramme of body weight A distinct im provement will be produced by the first injection, and complete disappear ance of primary or secondary lesions after two or at the most three, *injec* ... the secondary, or mor general opinion now ...

some, any of the prep of value in this disease *d extensively in recent* 14 milligrammes per

PLATE XIX (YAWS LESIONS)

Fourth picture shows the result of treatment

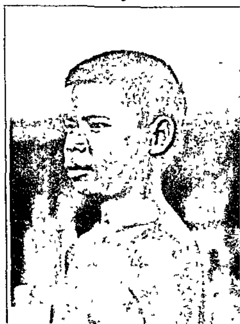


Fig 1



Fig 2





For young children, and when large numbers of persons have to treated in a short time or under difficult circumstances, intramuscular jections may be preferred by some workers The usual precautions rega ing the administration of these toxic drugs will, of course, have to be tak

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Whatever the treatment given, the aim should always be the reversal of a positive Wassermann or Kahn reaction

(d) **Subsidiary treatment** —For the tertiary lesions, some workers have used potassium iodide by mouth in large doses, either alone or in combination with arsenic and/or bismuth, they claim that a more rapid resolution *is brought about by this means*

For some of the tertiary lesions, *e g* the juxta-articular nodules, the contractures, and goundou, *surgical treatment will also be indicated*

Prognosis —Even when the condition is left untreated, spontaneous resolution will occur in a certain *percentage of cases in both the primary* (but probably rarely) and in the secondary stage, and the latter lesions usually last from six months to two years In neither of these stages does death ever occur as a direct result of the disease, and in both proper treatment will always produce a cure

* For penicillin therapy in yaws, see addendum, p 542

The lesions of the third stage may be life long in their effect and even if treatment is given there will usually be some permanent disabilities here again however death will seldom occur as a direct result of the lesions although quite often as an indirect one Death from septic pneumonia occurs sooner or later in most cases of gangosa

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PINTA

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EPIDEMIOLOGY

Geographical distribution —The disease has a limited tropical distribution in the western hemisphere the main countries affected are Colombia (4 per cent of the population) and Mexico (11 per cent) but it also occurs in Cuba and other islands of the West Indies Venezuela Ecuador Peru Brazil and Central America The endemicity of the disease has not been established in the eastern hemisphere though isolated and questionable cases have been reported from time to time in northern Africa Iraq India Malaya and the Philippines

The **age incidence** appears to vary in different countries and even in

so that superficial estimates indicate that the largest number are in the third and fourth decades whereas smaller and probably more accurate ones indicate an earlier age incidence

People of the dark skinned **races** seem to be more easily infected this is apparent in mixed populations

ÆTIOLOGY

Historical —The causal organism *Treponema carateum* was discovered by Doctors Trana and Armenteros, in the exudate from les ons and in the associated lymph

For young children, and when large numbers of persons have to be treated in a short time or under difficult circumstances, intramuscular injections may be preferred by some workers The usual precautions regarding the administration of these toxic drugs will, of course, have to be taken

(ii) The effect of bismuth injections is not immediate, *at least six injections at weekly intervals should be given* but distinct improvement will follow a smaller number Bismuth salicylate in a 10 per cent solution (dose up to 0 2 gramme), sodium potassium bismuth tartrate suspended in oil (dose up to 0 3 gramme), and precipitated bismuth suspended in oil to make a 10 per cent suspension (dose up to 0 2 gramme), have all been used with good effect The first injection should be about half the maximum dose and the dose should be increased by 0 5 c cm at each injection, children are given correspondingly smaller doses

A watch must be kept for stomatitis and albuminuria

Treatment with bismuth is unquestionably inferior to that with arsphenamine, but this form of treatment has the advantage of being very much cheaper There are several useful proprietary preparations of bismuth, *e g*, bismostab, and neotrepol, which will be convenient if a single case is to be treated, but by their use on a large scale much of the advantage of low cost is lost

(iii) There are several safe and effective arsenical preparations that can be given by mouth, *e g* stovarsol and carbarsone These must be given in the full therapeutic dose, 0 25 gramme twice daily for an adult, for 15 days, if further dosage is required, an interval should be allowed of about a month before a second course is started Good results have been obtained *with this treatment, but these oral drugs are definitely less effective than* the parenteral arsenic or bismuth

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ÆTIOLOGY

Historical —The causal organism *Treponema carateum* was discovered by Doctors Triana and Armenteros, in the exudate from lesions and in the associated lymph

For young children and when large numbers of persons have to b treated in a short time or under difficult circumstances intramuscular in jections may be preferred by some workers The usual precautions regard ing the administration of these toxic drugs will of course have to be taken

(ii) The effect of b ... th ...

jections at weekly

follow a smaller n

(dose up to 0 2 gr... ... bismuth tartrate suspended in oil (dose up to 0 3 gramme), and precipitated bismuth suspended in oi to make a 10 per cent suspension (dose up to 0 2 gramme), have all been used with good effect The first injection should be about half the maxi mum dose and the dose should be increased by 0 5 c cm at each injection children are given correspondingly smaller doses

A watch must be kept for stomatitis and albuminuria

Treatment ...

to be treated, but by their use on a larg

low cost is lost

(iii) There are several safe and effective arsenical preparations that can be given by mouth, e g stovarsol and carbarsone These must be given in the full therapeutic dose 0 25 gramme twice daily for an adult for 15 days, ...

month

with th

the parenteral arsenic or bismuth

Several combinations of these three forms of treatment have been suggested but probably the most effective is a course consisting of two in travenous neoarsphenamine and six intramuscular bismuth injections at weekly intervals the arsenic and bismuth injections being given coinci dently on the first two occasions the cost of such a course is not very high

To summarize for efficiency parenteral arsenic is the drug of choice for cheapness parenteral bismuth and for utility the special arsenical prep arations by mouth *

Whatever the treatment given, the aim should always be the reversal of a positive Wassermann or Kahn reaction

(d) ... *lesions some workers have* used i... s, either alone or in com binatio... im that a more rapid reso lution

For some of the tertiary lesions e g the juxta articular nodules the contractures and goundou surgical treatment will also be indicated

Prognosis—Even when the condition is left untreated spontaneous resolution will occur in a certain percentage of cases in both the primary (but probably rarely) and in the secondary stage and the latter lesions ... years In neither of these stages does ... the disease and in both proper treat

* ... addendum p 542

for referring to the former as tertiary and it is questionable if the latter are really pinta lesions, occurring as they do in populations in which both yaws and syphilis are common

Diagnosis —*Treponema carateum* can be found in scrapings from th

depigmented stage develops Thus neither the Wassermann reaction nor the finding of spirochætes helps in the differential diagnosis

From a clinical point of view, the difference between yaws and pinta is that the latter never causes true ulceration, nor the tertiary lesions commonly associated with yaws, although opinion on this latter point is not unanimous Pinta is also confined almost entirely to the dark-skinned races

Only gross ignorance of the clinical picture of both diseases could lead to confusion between pinta and leprosy

PREVENTION AND TREATMENT

The only effective prevention measures are education and treatment as in the case of yaws

The earlier lesions respond rapidly to anti syphilitic treatment (*also see* p 534) but a full course is often necessary to reverse a positive Wassermann reaction The atrophic and pigmented lesions will seldom respond

leucoderma

BEJEL*

Introduction—In 1928, while practising medicine in Deir el Zor, Syria Hudson drew attention to a non-venereal muco cutaneous treponematosis encountered among the nomadic tribes in Arab countries this condition is known as *bejel* in Iraq and Syria *firjal* and *latta* in Palestine, *laghout* in Lebanon and *jirar* in Trans-Jordan

Hudson (*loc cit*) at first described the disease as a distinct entity, but has modified his views recently (Hudson 1937 1938), and is now inclined to support Hasselmann s

he (Hudson 1941) has gone ev

is a modified form of syphilis

of view he considers that syph

clinical entities It is not unlikely that originally all four causal organisms developed from a common source, but it seems more probable that bejel was historically the earliest of the treponematoses from which these other diseases evolved

Geographical distribution—Whereas yaws is a tropical condition which is always associated with abundance of vegetation humidity and

* By Harry Senekjie M D M S Assistant Professor of Tropical Medicine Tulane Medical School The published papers on this disease are very contradictory and as Dr Senekjie has had at least six years experience in the countries where this disease occurs the author asked him to contribute this section

nodules of a case of pinta in Havana Cuba in August 1938 This finding was con

The **causal organism**, *Treponema carateum*, is morphologically very
measurements,
out 17 microns,
a flexible spiro
at about one
early papular
lesions, but are very scanty in the later dyschromatic and depigmented lesions

As the exudates from all the early lesions contain treponemata which, as in the case of yaws, can enter the new host through a small skin abrasion direct **transmission** is possible, therefore direct contact is probably the usual method of transmission But it has also been shown that certain flies, *e g Hippelates pallipes* and *Simulium hæmatopotum*, are capable of mechanically conveying viable spirochætes, and it is therefore possible that these and other flies also play some part in transmission, in places where

SYMPTOMATOLOGY AND PATHOLOGY

After an incubation period of 7 to 20 days a small papule appears at the point of entry of the infection Within a few days further papules appear around the first one, and an erythemato-squamous patch develops This scaly patch is slightly raised above the skin surface and is variously shaped but usually more-or-less round and anything up to an inch and a half in diameter It takes four to seven weeks for it to attain full development, when it becomes a chronic, irritating but non-ulcerating lesion

The particular pathological characteristic of the pinta lesion is at first a stimulation of the cells of the melanoblastic layer and later their destruction, so that there is at first hyperpigmentation, a characteristic dark coppery pigmentation of the skin, usually on the face, but also on other parts of the body, and later, atropic lesions with leucoderma, or vitiligo The explanation for the dyschromatic effects that are sometimes seen is
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papules appear on the trunk extremities groin and genitalia and develop into circinate and rarely roseolar eruptions As there is never a history of anything corresponding to the primary chancre of syphilis it seems probable that these constitute the primary lesions

There are no constitutional symptoms and no pain or pruritis in association with these early lesions and apparently the health of the child is not impaired These lesions disappear spontaneously without leaving any scar and often without any treatment

A latent period is followed by the appearance of the late lesions which are usually ulcerative in character A small erythematous patch appears in the soft tissues of the mouth this breaks down and spreads to the soft palate tonsil or pharynx so that swallowing becomes painful Leuco plakial patches may be observed in the mouth After several months the lesion heals with the formation of scar tissue Sometimes the process extends to the larynx and produces changes in the voice or hoarseness or even stridor due to the contraction of the cicatrix Similarly the ulcerative lesions of the nose may destroy the soft tissues and even erode through the hard palate into the mouth and maxillary sinuses producing a gangosa like condition and rarely paranasal swellings resembling goundou develop

The characteristic skin lesions begin as papules and then ulcerate these granulomatous ulcers heal in one place while spreading in another and at times fungating masses result that become covered with crusts and exude a sero sanguineous or purulent discharge

Hyperkeratosis of the soles of the feet either localized at sites which bear weight or generalized with extensive fissures are common findings There are similar lesions of the palms Sometimes depigmented areas appear on the skin and there may be alopecia (Hudson 1936)

Periosteitis and osteitis especially of the long bones frequently occur patients complain of throbbing bone pains and sometimes the small bones of the hands are involved Juxta articular nodules around the knee ankle and back are seen These are painless movable hard masses which do not have any tendency for ulceration but may become fibrosed (Hud son 1935)

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Apparently there are no cardio vascular symptoms but occasionally

general paralysis are rare among Arabs

TREATMENT

The specific treatment of el once is neoarsphenamine It must how ever be remembered that the Arab cannot tolerate large doses of arsen icals Bismuth comes next in its effectiveness while mercury also gives very satisfactory results A much shorter course of treatment than that given for syphilis is necessary

rainfall, bejel occurs in dry and hot climates mainly in desert areas It ha

nomadic Arabs, though up to the present no confirmatory reports hav been received from these areas

EPIDEMIOLOGY AND TRANSMISSION

A very high percentage of the people of all social strata in infecte nomad Arab tribes suffer from the disease It is usually acquired in earl infancy or childhood, but when children escape infection, they will fre quently become infected in later life Although venereal transmission i possible, the infection is usually transmitted non-venereally Promiscuou sexual intercourse is uncommon in these tribes, but cups, glasses plates and towels are shared freely by the members of not only one, but of several families

During certain seasons flies are very prevalent and, just as yaws is apparently transmitted by *Hippelates pallipes* and pinta by *Simulium hæmatopotum*, so bejel may be transmitted mechanically by house-flies

Unlike syphilis, but like yaws and pinta, bejel is never transmitted congenitally

ÆTIOLOGY

The causal organism is morphologically indistinguishable from *Treponema pallidum*, *T pertenue*, and *T carateum* but, in the writer's opinion it is more flexible The spirochæte is found easily in early lesions, but is very scanty in the late lesions, the former are presumably the most infectious Attempts to infect rabbits, guinea pigs, and mice intradermally have so far failed

Immunity.—There is no natural immunity to bejel, and persons of all ages and races are apparently susceptible, but immunity can be acquired through previous infection, thus, most adult Arabs are immune through infection in childhood The Wassermann, Kolmer and Kahn reactions are constantly positive in this disease

The question of cross immunity between bejel, and syphilis, yaws and pinta has not yet been settled, but the writer has seen syphilitic chancre develop in Arabs who had had bejel and who showed a positive Kahn reaction

PATHOLOGY

This has not been studied to the same extent as in the other treponematoses, but it is evident that this disease is an epiblastotropic one, like yaws and pinta, rather than a panblastotropic one, like syphilis

The skin lesions are characteristically granulomatous ones

SYMPTOMATOLOGY

The initial lesions are usually in or around the mouth, however, in those rare cases where the infection is venereal the lesions are naturally on the genitalia These initial lesions are usually patches which desquamate but do not ulcerate The usual location is the lips, angles of the mouth, tongue, mucosa of cheeks, rarely the glans penis, labia, or mucosa of the vagina At the same time, or sometimes after a short interval,

papules appear on the trunk extremities groin and genitalia and develop into circinate and rarely roseolar eruptions As there is never a history of anything corresponding to the primary chancre of syphilis it seems probable that these constitute the primary lesions

There are no constitutional symptoms and no pain or pruritis in association with these early lesions and apparently the health of the child is not impaired These lesions disappear spontaneously without leaving any scar and often without any treatment

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TREATMENT

The specific treatment of choice is neoarsphenamine It must however be remembered that the Arab cannot tolerate large doses of arsenicals Bismuth comes next in its effectiveness while mercury also gives very satisfactory results A much shorter course of treatment than that given for syphilis is necessary

Prevention —The most effective means will be by education and propaganda amongst the tribesmen, combined with a treatment campaign particularly amongst the children Bismuth is the most practical drug for this on account of its relatively low cost and long continued action, but arsphenamine is more potent

PROGNOSIS

This is good In many cases a spontaneous clinical remission will occur without treatment, and the response to anti syphilitic treatment is excellent

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Addendum —Penicillin is very effective in the treatment of yaws and will very probably prove to be the drug of choice for any of these three spirochætoses when cost is not important A total dose of 500,000 units given over a period of 5 or 6 days will effect a cure

TROPICAL SKIN ULCERATIONS

Introduction —There are many types of skin ulceration that will be encountered as frequently in a temperate as in a tropical climate specific ulcers *e g* syphilitic tuberculosis actinomycotic and glanders ulcers associated with systemic or blood diseases such as diabetes sprue pellagra sickle celled anæmia and purpuric conditions non specific ulcers associated with varicose veins and septic ulcers secondary to skin diseases wounds abrasions and insect bites

However skin ulceration is both commoner and more chronic in the tropics than in the temperate zones This is in part because many specific parasitic infections are peculiar to the tropics but also because insect bites and the subsequent self inflicted trauma so frequently cause breaches in the integument because the high temperature often associated with high humidity encourages the growth of bacteria on and in the skin and its glands and appendages and because there are so many systemic infections and dietary deficiencies to lower the tissues resistance to invasion The multiplicity of the predisposing conditions and superimposed infections tends to produce ulcers of such a wide variety that a description of all of them is out of the question

The ulcers especially associated with the tropics that have been described or will be described in other sections include the cutaneous leishmaniases oriental sore (p 179) and espundia (p 191) leprosy (p 481) yaws (p 523) cutaneous amœbiasis (p 435) tularæmia (p 345) rat bite fever (p 237) tsutsugamushi disease (p 275) and the venereal ulcerations lymphopathia venereum (p 562) and granuloma venereum (p 568) as well as the secondary ulcerations of bubonic plague and the rare cellulocutaneous type of septicæmic plague (p 335)

This leaves two tropical skin ulcerations that do not fall naturally into any other section namely ulcus tropicum or Naga sore and veldt sore

ULCUS TROPICUM

Definition —Ulcus tropicum *)
is a troublesome lesion that oc ld
workers in humid tropical clim at
least by an anærobic fusiform bacillus

Geographical distribution —Ulcus tropicum occurs in many tropical countries but the majority of the earlier reports on this condition came from Africa and India It is also common in tropical America

EPIDEMIOLOGY

It occurs almost exclusively in hot damp climates and amongst farmers and field workers It is more commonly *reported* amongst labour forces *e g* tea plantation workers in such countries but this is probably because of the financial loss to employers entailed as there is evidence that private cultivators also often suffer from the condition Recently a num

* The word phagedænic (literally meaning eating canker or spreading ulcer) is

ber of British and Indian soldiers in Assam have suffered from somewhat similar sores, but it seems questionable whether these sores have the same ætiology

The disease occurs not only among men, but women and children are also susceptible in those population groups where both sexes work in the fields

In the tea-estate labour forces in India, ulcus tropicum reaches its

There is a marked variation in the incidence from year to year in any one locality, this has been particularly noticeable on tea-estates

ÆTIOLOGY

A number of theories as to the cause of this condition have been put forward, with reference to which it is easier to be critical than constructive

The subject can best be discussed under three headings, the predisposing factor, the specific organism, and the determining factor

(a) The predisposing factors.—There has been a strong tendency in recent years to attribute tropical ulcer to dietary deficiency, in whole or in part The present [illegible]
the point of view o
should be considerec
experience in Papu
suffered more than

Papers in which dietary deficiency is incriminated have never been very convincing or very specific in their indications as to which particular dietary element is the determining one, several vitamins and calcium have been named Further, many instances of the infection—natural, experimental and accidental—of well-nourished persons have been reported
of the epidemiology
and even probably,

Again, it would seem not unreasonable to suggest that debilitating diseases may reduce the individual's resistance against the invading organisms, and standard tropical infections such as malaria, dysentery and ancylostomiasis have naturally been selected, in fact at one time these

(b) The specific organisms.—The frequency with which a fusiform bacillus alone or the fusiform bacillus *plus* a spirochæte are found in the

avoid taking sides in this controversy, refer to the condition as fusospiro-

* Charters (1943) has produced further evidence to support the dietary-deficiency theory He considers that vitamin A is the deficient element

chætosis In India, we have found that the fusiform bacillus is constantly present and that there is always another organism almost equally prominent in the field, this is, however, not always a spirochæte but is quite often a diphtheroid This view is not incompatible with the unitarian theory referred to above, as, in the instances in which there were no spirochætes in the ulcers, it may simply have meant that on account of some local condition in the ulcer all organisms were in the fusiform stage

The proof of the causal association of these organisms is not complete as it has never been possible to induce an ulcer with a pure culture of any of them, although this has been done frequently with mixed organisms from an ulcer, and with a mixed culture of *Bacillus fusiformis* and [illegible]

The fusiform bacillus is about 17 microns in length and 1 micron in thickness, it is fusiform in shape, as its name implies, and it stains well with Romanowsky stains, usually showing a slightly beaded appearance It is gram-negative

It is an anærobe and can be grown on gelatin-serum agar It would however, be surprising if in the many tropical countries in which an apparently similar ulcer appears there were not more than one specific organism concerned

The Klebs-Loeffler bacillus has on several occasions been isolated from a clinically typical Naga sore

(c) The determining factors—There seems to be very little doubt that some breach in the epithelium is essential to allow the organisms to gain entry Four common causes are —(i) injury, (ii) dermatitis, (iii) insect or leech bite, and (iv) 'water sores' (ancylostoma invasion) The ulcer appears most commonly on the legs and feet at points most subject to injury in those who walk about bare legged, on areas of skin likely to be affected by dermatitis as a result of coming in contact with irritant plants, chemical manures, etc, or at points where hookworm larvæ often enter and cause vesiculation Panja and Acton (Acton, 1932) showed experimentally that it was easier to produce an ulcer on the leg than on the arm in the latter situation, a sore formed but healed rapidly, whereas in the former it developed into a typical ulcer

It is often found that occupational groups particularly subject to local injury, *e g* tea-garden coolies working amongst tea bushes suffer more than their fellow coolies who work in the factory, and even amongst Clements' Papuan natives (*vide supra*) the factor may have been occupation rather than diet

The source and transmission of the causal organism—The fusiform organism is found infecting the mouth and other mucous membranes, but it also occurs widely in nature as a saprophyte and is commonly found in the soil The ulcers appear in outbreaks in which a large number of persons are affected about the same time, but it has never been satisfac-
- directly
nological
n source

Insects have been suspected as vectors, but there is no indication that they act otherwise than as mechanical transmitters, the common house-fly and flies of the genus *Siphunculina* have been particularly sus-

pected Flies of the latter group are very prevalent during the season at which these ulcers occur, and they are certainly attracted to purulent wounds but they have never been incriminated experimentally and some negative observations have been made It is almost certain that flies *could* act as mechanical transmitters how far they are responsible for outbreaks is uncertain and there is little positive supporting evidence for the hypothesis

Roy (1928) suggested that the bacillus probably remains in the soil just below the surface during the dry season and that when the first monsoon rains convert the surface soil into mud which is splashed and caked over the legs of the coolies or cultivators anaerobic fusiform bacilli, which are imbedded in the mud infect existing skin wounds Later when the rains become heavy the bacilli are washed out of the soil The present writer feels that this theory fits many of the known facts regarding the epidemiology of the disease It seems quite possible that the variations in the incidence of ulcus tropicum from year to year might be accounted for by variations in climatic conditions or in the use of manures which will alter the soil flora

PATHOLOGY

The fusiform bacillus is unable to establish itself without the cooperation of some other organism the membrane producing diphtheroids appear to be amongst the most suitable symbionts The fusiform anærobes multiply rapidly under the protecting membrane and establish themselves in subcutaneous tissues they have limited powers of tissue invasion but they produce a toxin that causes necrosis of the overlying skin and a cellular reaction in the surrounding tissues Later there is granulation tissue formation at the edges and at the base of the ulcer under the layer of fusiform bacilli which form a thick mat immediately under the upper necrotic layer of the ulcer this granulation tissue is later replaced to some extent by fibrotic tissue There is some indication that the individual ulcer is anatomically self limiting as the ulcer tends to be circular and not more than an inch or two inches in diameter its downward extension is limited by the first fascial layer that it encounters and its lateral extension by a ring of cellular reaction and eventually by the fibrosis that occurs There are of course, occasions when two or several separate ulcers join to form a large and sometimes irregular shaped ulcer which may almost surround the leg interfere with the circulation and lymph drainage and cause painful œdema of the leg and foot There is no evidence of hæmatogenous or lymphatic extension although the proximal lymph nodes may enlarge as a result of infection of the wound with septic organisms

SYMPTOMATOLOGY

Small itching papules appearing at the site of an existing scratch or abrasion rapidly become necrotic and if the necrotic tissue is removed a *small ulcer with undermined edges will be found underneath* *The ulcer* spreads rapidly and in a few days will have reached the standard size (*vide supra*) a circular ulcer from an inch to two inches in diameter Other ulcers may meanwhile be developing in the neighbourhood these may remain discrete or may coalesce and form a large ulcer In a large percentage of cases there is however only a single circular ulcer

The ulcers are usually on the lower limbs on the dorsum of the foot at the ankle or instep or on the front of the leg a few inches above the instep they rarely occur above the knee

Mild constitutional symptoms of a toxæmic rather than a febrile nature often accompany the ulcers Even deep ulcers may not be particularly painful, provided they do not interfere with the blood supply or lymph drainage, but when this occurs the swelling, heaviness, and pain make the patient unable, or at least disinclined to do his work

In those cases in which the Klebs-Loeffler bacillus has been found, the neuritic sequelæ associated with this infection will often be observed (see VELDT SORE)

The discharge is usually a reddish watery exudate that trickles continuously from under the necrotic membrane that covers the ulcer The edges of the ulcer at first are undermined, but later become firm, fibrotic, and raised The ulcer extends down to the first fascial layer or to the bone, but the ordinary tropical ulcer does not usually involve the bone or the joints, however, the danger to joints from the presence of a large open septic wound in their vicinity is obvious, and in many cases the septic infection does extend to the tendon sheaths and joints, producing a dangerous condition at the time and serious crippling afterwards

The ulcers are usually very chronic but even without any special form of treatment most of them will heal in a few months time, in Assam, for example, when the rains stop and the weather becomes cool again They leave a considerable scar Any immunity built up can only be very temporary as it is not uncommon for a patient to suffer from these ulcers at about the same season year after year

DIAGNOSIS

When tropical ulcers presenting the typical picture—circular sloughing ulcers with a firm raised edge [illegible] mostly below the knee—are seen ag[illegible] ulcer is encountered in other circum- [illegible] from other causes and finally resort to bacteriological examination

Other conditions that have to be excluded are varicose ulcers (not common in the class of patient who is likely to suffer from tropical ulcer), syphilitic ulcers (which can be excluded by a negative Wassermann reaction), yaws (which can also be excluded by a negative Wassermann reaction and by failure to find *Treponema pertenue* in smears from the ulcer), oriental sore (which has a very different geographical distribution and is confined to drier climates, and will show the round forms of *Leishmania tropica* in material taken from the edges of the ulcers, see p 185), and veldt sore

If a smear is made from the exudate, or better still from a scraping from the base of the ulcer, the characteristic fusiform bacilli, with or without spirochætes will be recognized easily In a Giemsa-stained specimen, the characteristic beading of the fusiform bacilli will be clearly seen

PREVENTION

As there is still some uncertainty about the cause of ulcus tropicum, measures to prevent it cannot yet be placed on a proper scientific basis, but, if meanwhile we adopt certain premises, it will be possible to map

out a provisional preventive programme These premises are that the ulcers are most likely to occur in people who are ill-nourished and/or debilitated from diseases such as malaria and dysentery, that the causal organism—which is apparently a fusiform anærobic bacillus—in nature lives as a saprophyte, probably in the soil, and that an epidermal lesion, due to trauma, dermatitis, water sores, insect or leech bite, or to some other cause, is essential for the specific organism or organisms to gain entry Preventive measures should therefore include, (a) improvement of the diet and general state of health of the population, (b) the protection of the limbs against direct contact with the soil or mud and the early cleansing of the skin thus contaminated, (c) protection of the legs from trauma, contact with irritant plants, and insect and leech bites, and the prevention of hookworm infection and of dermatitis from any cause

How these recommendations are to be put into practice will depend so much on local conditions that detailed discussion here is out of the question Very careful consideration should, however, be given before any [illegible] the most promising theoretical recom-[illegible]mag' The point can possibly be best [illegible]nendations made on *a priori* grounds

(i) *Recommendation* That a shallow concrete reservoir containing antiseptic lotion 16 inches deep be placed so that bare-footed tea garden coolies returning from work have to walk through the tank and cleanse their legs

Result If the [illegible]

mental

(ii) *Recommendation* That tea-estate coolies should be provided with putties to protect their legs from scratches which they are very liable to get from the pruned tea bushes

Result Very early in the day the putties became saturated with rain and mud, and the wearing of damp putties for the rest of the day caused dermatitis

It is possible that in certain circumstances both these recommendations might have been successful, but in most cases they were a failure, apparently for the reasons given above

The encouragement and if necessary supervision of individual cleansing of the feet of coolies on return from work, and the early treatment of all skin lesions may necessitate the temporary employment of considerable extra personnel on a tea-estate, but may be well worth undertaking if the efficiency of the labour force is seriously threatened at a time of year when most labour is needed, as often happens when there is a serious outbreak

TREATMENT

There is no short cut to the successful treatment of this condition, as is evident by the multiplicity and the variety of the methods advocated Nearly every writer on the subject has some special treatment that he considers the best. In view of the possibility that the name 'ulcus tropicum' is used to describe an ætiologically heterogeneous group of ulcers, short accounts of some of the treatments advocated by reliable observers will be included

Some Treatments Advocated

'Specifics'.—Parenteral arsenicals, arsphenamine, neoarsphenamine and novarsenobenzol, can claim the largest number of advocates Various bismuth preparations have also been used with apparent success

Sodium iodide given by mouth in doses up the point of producing iodism, *combined with local applications of hydrogen peroxide*, has had some success For sulphanilamide and sulphathiazole, good results have been claimed by some workers, and denied by others

A number of workers have advocated autogenous and specific stock vaccines prepared by various methods, but others consider that equally good results are obtained by non-specific vaccines, and yet others have *recommended milk injections*

Under this heading also, the specific action of calcium and of several vitamins, that have been claimed by some—usually isolated—workers should be mentioned

Local applications.—Neoarsphenamine and other arsenicals and sulphanilamide and sulphathiazole have been *recommended as local applications* A saturated solution of potassium permanganate (5 per cent) applied by means of a shaped piece of soaked lint to the ulcerated area, only for as long as the patient can stand it, pure phenol or powdered copper sulphate in glycerine (one part in two) similarly applied, crude tar, and powdered cinchona febrifuge, have each been advocated More recently, whole blood, serum, and powdered dry plasma have been suggested as dressings Some success has been claimed for cod-liver oil dressings

For bathing the ulcers acriflavine, 1 in 1000, potassium permanganate, 1 in 4000, and electrolytic chlorogen have been advocated Innumerable creams, ointments and dusting powders, in the preparation of which zinc oxide, several bismuth salts, iodine, iodiform, and/or sodium hypochlorite, are combined with olive oil, paraffin or lanolin or boric acid have been suggested

Surgical procedures, from débridement to total excision of the ulcer, have been proposed

PRACTICAL CONSIDERATIONS

In considering the treatment of this condition, it is very necessary to keep the practical aspects of the problem before one There will, of course, be other circumstances, but a common one will be that in which *a large number of coolies in a labour force are suffering* from these ulcers and *the immediate requirement* is to get them on to their feet again in the shortest time possible In most cases it will pay in the long run to put the patient into hospital (and there will usually be some sort of hospital, however primitive) and treat him thoroughly, rather than to apply palliative measures

The patient must be kept lying down as much as possible The wound *must be thoroughly* cleansed, first with hot magnesium sulphate fomentations then preferably with hydrogen peroxide, and finally with some anti- [illegible] dead [illegible]

The ulcer itself is then very [illegible]
a mixture of copper sulphate and phenol in glycerine (half an ounce pow-

dered copper sulphate in one ounce of glycerine to which a drachm of phenol is added), this is allowed to act for a few minutes and is then washed off with normal or hypertonic saline, finally, it is dusted over with sulphonamide, covered lightly with a single or a double layer of gauze to keep off dust and flies but to allow as much air and sunlight as possible to get to the ulcer, the latter appears to have a very beneficial effect in some cases This is repeated for several days until a healthy red healing surface is left One or two applications of scarlet-red lotion may help the healing process After a week or ten days, it will often be possible to cover the area with *tulle gras*, or some such dressing, strap the whole limb firmly or even put on a plaster-of paris casing, and allow the patient to go back to work

In some cases ambulatory treatment along these lines will be possible In such cases the phenol 'cauterization' should be very thorough and the strapping or ... a week or more Some workers claim ... nding skin only, putting on a piece o ... ipping or plaster immediately

Older ulcers with thick fibrous edges will require surgical scraping This should be done under an anæsthetic and should be thorough, it will also be advisable to swab the ulcer with phenol to complete the operation

If the area is extensive, skin grafting will be necessary

During his stay in hospital the patient should be given a good balanced diet, with a full quota of protein and additional vitamins if there are any other indications of specific deficiency

In cases in which the presence of the Klebs Loeffler bacillus is established specific treatment as for veldt sore should also be given (*vida infra*)

PROGNOSIS

Left untreated a certain percentage of ulcers will heal in a month or so, but the majority will continue for several months, even up to a year or more

Under active treatment early ulcers should keep the patient away from work for a few days only, more advanced ones for two to three weeks, and very advanced ulcers for two to three months A few obstinate cases will be encountered that will lead to the loss of a limb and death may follow septic complications

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VELDT SORE

Definition—Veldt sore is a shallow ulcer appearing on exposed parts of the body that affects white persons, mainly, in hot desert areas, the Klebs-Loeffler bacillus is recoverable from the lesion in a large percentage of cases

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Skin infection with the Klebs-L

Geographical Distribution—The condition has been reported from a number of localities, mainly in the subtropics where desert conditions prevail, South Australia (Barcoo river), Queensland, North Africa, including Egypt, and the Sudan, South Africa, Gallipoli, Arabia and Iraq, and northern India

EPIDEMIOLOGY

The disease is largely confined to sojourners in hot desert areas, *e g* Australians in the Barcoo rivers area, it was prevalent amongst British soldiers in South Africa in 1899-1901, amongst the colonial and British troops in Gallipoli, Egypt, and Iraq in 1914-1918, and recently amongst the soldiers of the United Nations in North Africa

It is more common amongst fair-haired than dark-haired, and commonest amongst red-haired individuals, it does apparently occur amongst the fairer-skinned natives of the endemic areas, *e g*, the Arabs of Iraq, but is not common amongst these and is even rarer amongst darker-skinned Africans and Indians

ÆTIOLOGY

Historical—Walshe (1918) noted the association of these sores with diphtheritic paralysis and Craig (1919) demonstrated the presence of Klebs-Loeffler bacilli in the ulcers

Klebs-Loeffler bacilli, *Corynebacterium diphtheriæ*, are recoverable from the well-established ulcer in a large majority of cases In the pre-ulcerative (vesicular) stage, it is not usually found This suggests that the lesion in its early stages has some independent cause and that the diphtheria bacillus is superimposed and gives the ulcer its special character, particularly its chronicity

PATHOLOGY AND SYMPTOMATOLOGY

The lesions usually appear on exposed and hairy parts of the body (although not usually on the head) on the dorsa of the feet, on the knees, on the backs of the hand, on the forearms, and on face, neck, and ears

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durated and the base of the ulcer which is still shallow is covered with a greyish slough the surrounding skin is cyanosed rather than inflamed and there is not usually much exudate The lymphatic involvement is not constant and probably depends on the nature of the secondary invading organisms

The special character of the lesions is their obstinate chronicity and their failure to respond to any of the usual treatments for septic sores They may heal temporarily with a thin epithelial covering which is likely to break down and even when they finally heal they leave a depressed scar that may persist for years

From the outset the lesion is a painful one at first the sensation is that of pricking and itching then burning and finally there is a frank pain There are usually some constitutional symptoms fever, headache and malaise

Very common symptomatic associations with these ulcers which in one reported s

s are
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encountered or if the sore is on the upper limb loss of power of grip loss of tactile sensation and inability to execute any fine movements of the hand Later the toxin reaches the circulation and more distant groups of muscles are affected such as the muscles of visual accommodation and of the palate

The nervous symptoms do not usually develop for some weeks after the ulcers first appear and in fact it is often several weeks after the ulcers have healed before the eye symptoms develop

DIAGNOSIS

This is made on clinical and epidemiological on bacteriological grounds or on both

The investigator must first decide for himself what in his opinion constitutes a veldt sore He may decide to accept the clin cal n ture and
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or Burma and starting perhaps as leech bites which give an culture of *C diphtheriæ*

The writer feels that the first attitude is the correct one to present Veldt sore was a clinical entity for many years then Loeffler bacillus was associated with it The Klebs Loeffler

been shown to be promiscuous in its associations It does not seem log to the writer that this bacillus should be allowed to take the name vi into the humid jungles of Assam and Burma

A bacteriological diagnosis is made by direct smears (stained w Loeffler's methylene blue), cultures, fermentation reactions and ani inoculations (to determine the virulence)

PREVENTION

The initial sores can to some extent be prevented by giving expo persons protection from the sun, by suitable clothing and protecting o ments (see p 45), and from the irritating effects of sand and other trau also by clothing and by frequent bathing, and, in view of the poss effect of diet, one must add, by the giving of a balanced diet rich in vitam

The superimposition of the diphtheritic infection can be prevented early treatment and the protection of all sores and abrasions, and in case of troops or other communities, by the discovery and suitable tre ment of all diphtheria carriers

A person with infected ulcers should also be isolated to prevent t spreading of infection It is possible for a patient to develop a fauc infection from his own ulcer, as well as *vice versa*

Protection of the community by diphtheria toxoid may be indica in special circumstances

TREATMENT

The treatment of the early sores need not be discussed here, howev when the Klebs-Loeffler bacillus is implanted in the wound, anti-diphth itic serum becomes a specific The serum is applied directly to the wour and about 20 000 units given intramuscularly, with the usual precautio In some instances the effect on the local lesion appears to be dramatic b anti serum is in any case necessary, in order to obviate or control t neuritic sequelæ

Topical applications of penicillin (250 Oxford units per c cm) has r cently been used with success

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LYMPHOPATHIA VENEREUM

Definition.—Lymphopathia venereum (*syn* lymphogranuloma inguinale and poradenitis) is a disease of venereal origin, caused by a filtrable virus which produces at the point of entry a primary sore that is frequently overlooked, infection of the inguinal glands in men and the pelvic glands in women, and a series of conditions that have in the past been known severally as 'climatic bubo', 'esthiomene or ulcer and elephantiasis of the genitals', 'genito recto-anal syndrome' and 'inflammatory stricture of the rectum'

Historical.—Climatic bubo has for many years been recognised as a venereal condition common amongst and apparently peculiar to sailors who have visited oriental and other tropical ports it was thus named by Godding in 1896 Materially the same condition but one with a slightly wider incidence was later described by Durand Nicolas & Favre (1913) and the condition became known in France as

Nicolas-Favre disease The troublesome chronic ulceration and elephantiasis o the female pudenda sometimes associated with rectal stricture and proctitis ha been known to gynæcologists for nearly a hundred years (Huguier 1849) a

EPIDEMIOLOGY

Geographical distribution —It has a world wide distribution but it is undoubtedly much more common in tropical countries, this is probably less a matter of climate than of social conditions *(vide infra)*

Social, sex and race distribution —It is a venereal disease It is particularly associated with the low class prostitutes that frequent dock *areas in most countries in the world The disease is very prevalent in* Mediterranean, South American and Eastern ports, where such prosti tutes abound and where little or no control is exercised over them

In a woman evidence of the disease will often be concealed so that she may be unconscious of the infection and transmit it to a number of men, men are therefore more frequently affected Further, for the same reason men will be more likely to seek medical advice and the sex dis parity will be exaggerated

cent of the outpatient population Further, Frei s test surveys indicate *that a high percentage of the negro patients at venereal clinics suffer from* this infection without necessarily showing any symptoms

ÆTIOLOGY

Historical —In 1924 Gamna described certain chromatin-staining bodies as ... the lesion of lymphogranuloma ingui ... erstrom ... n Japa ... granulo- ... 34) are

actually the virus

The **causal organism** is a filtrable virus between 0 127 micron and 0 175 *micron in* diameter, it passes through Seitz E and K, Chamberland 1, 2 and 3 and Berkefeld V and N filters It is transmissible to most laboratory animals except rats Mice are the most suitable experimental animals in these animals an encephalitis is produced and from the brains of infected mice antigen *has been prepared for Frei s test* It grows on the yolk sacs of developing chick embyros and from this source also an antigen has been prepared

PATHOLOGY

The virus gains entry through a small abrasion in the skin or mucous membrane or possibly through the intact epithelium, usually of the prepuce or glans *penis in men* and of the vagina or the cervix in women but in

the latter the primary sore may be on or near the clitoris, in the fourchette or on the labia Primary lesions around the anus and on the lips have been attributed to unnatural practices Extra genital primary lesions have also occurred in children, the infection having been transmitted by contact with bed companions

There is little local reaction The epidermis becomes slightly thickened, but there is no downgrowth into the papillary layer There is no granulomatous reaction, but some infiltration of plasma cells, lymphocytes, and polymorphonuclears, and some exudation which raises the superficial layers and produces a nodule, a papule, or just vesiculation The papules break down or the vesicles burst leaving a shallow abrasion which may be surrounded by a narrow band of hyperæmia but little infiltration

Thence the virus passes along the lymphatics to reach the first group of lymph nodes In the case of men, this will be the inguinal glands, this will also be the case in women in whom the primary sore was in the anterior part of the vulva, but this is rare as the lesion is more often in the vagina, and from here the infection is carried to the lymphatics in the wall of the anal canal and lower end of the rectum, and then by reflux infection to the deep pelvic glands, which include the peri-rectal and retroperitoneal The wall of the lower end of the rectum and anal canal becomes thickened and later contracts causing a stricture

In the glands, pin-point epithelioid formations, with giant cells and large reticulo-endothelial cells appear The centres become necrotic and [illegible]

form Around the gland there is a plastic peri-adenitis Several of these stellate necrotic areas coalesce and form an abscess, which then becomes secondarily infected and suppurates, or it may dry up and become partly absorbed, but fibrotic changes occur in the surrounding tissue, and scars form and eventually contract

Suppuration is usually the fate of the superficial, inguinal glands, the pus tracks to the surface leaving a number of sinuses which are further infected and become chronic However the deep pelvic and peri-rectal glands seldom suppurate, but during the healing process there is a considerable amount of fibrotic contracture which may cause a stricture of the rectum at a higher level than that referred to above

[illegible]

vide), so that the final state is often one of chronic ulceration

There are thus four stages in the pathogenesis of this infection, namely,

(i) *the symptomless stage of invasion,*

(ii) *the primary lesion,*

(iii) *the invasion of the lymphatic glands, and*

(iv) *the sequelæ, due to the fibrotic changes in or around the glands, causing rectal stricture and/or lymphatic obstruction with elephantiasis and ulceration*

The Blood—There is no characteristic blood picture, but in the majority of cases there is a moderate leucocytosis with a relative large mononuclear increase, later, there may be a normal white-cell count with a slight relative lymphocytosis

There is an increase in the sedimentation rate, and a marked lowering, or even an inversion, of the albumin/globulin ratio, to the extent of causing a positive aldehyde test (see p 164) in rare cases

SYMPTOMATOLOGY

The symptomatology can best be considered under four headings corresponding to the four stages in pathogenesis enumerated above

(i) **Incubation period**—From the time of exposure to infection to the first appearance of the primary sore is only a few days, but if this is missed it may be a month or more before the other lesions reach the clinical stage

(ii) **The primary sore**—This commences in the localities noted above as a vesicle or cluster of vesicles which burst and leave a small shallow ulcer with a white or greyish base and clean cut edges surrounded by a narrow band of slightly reddened skin which is not indurated, it is usually painless, it heals rapidly, and it leaves no scar

In some areas, it may be possible to trace the lymphatic spread by feeling a cord like lymphatic vessel, *e g* along the wall of the vagina and in these cases nodules may form along the course of the lymphatic vessel and may later break down

(iii) **The secondary phase**—The onset of this phase is usually from two to six weeks after the initial infection and often occurs with marked constitutional symptoms, fever, headache, arthralgia and malaise The fever which may be high does not follow any specific pattern, and may be mistaken for that of typhoid plague, or other febrile disease, it may fall when the buboes develop, or continue and eventually become a septic type of fever as the buboes suppurate Rashes and skin eruptions, eye changes and other symptoms suggestive of an allergic reaction may occur

The buboes which are frequently bilateral, are at first soft and rubbery, discrete and slightly tender, later, they become matted, adherent to the underlying tissues and to the skin and very tender If they are felt carefully, soft fluctuating points will be identified They may heal spontaneously leaving a dimple where the skin has been caught in the retracting scar tissue, but, as indicated above, the inguinal glands usually become secondarily infected suppurate and, if they are not opened discharge through one or more sinuses Sometimes further secondary infection causes sloughing of the skin and an open ulcer is formed which is usually very chronic The iliac glands may be affected and although these are much less likely to suppurate, it is often possible to feel the large mass of enlarged glands in the iliac region

In women when the pelvic glands are infected there will often be no localizing signs accompanying the febrile attack to indicate its nature except possibly a heaviness in the pelvis, some low back pain, and dyspareunia

(iv) **The tertiary phase**—There will be an interval of several months to several years before the next phase becomes established The symptoms

of rectal stricture are usually frank dysentery (i e the passage of blood and mucus) or alternate diarrhœa and constipation as in carcinoma recti The stricture can be seen through the sigmoidoscope with an inch or so of ulcerated and sometimes necrotic mucous membrane below and there is almost certainly (although it cannot be seen) several inches of ulcerated bowel above the stricture to account for the blood pus and mucus coming through the stricture opening and for the associated pain and tenderness

anus Ulcers develop and spread involving all the soft parts which break

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DIAGNOSIS

The clinical diagnosis in the well-developed and typical case should not present any difficulty but there will be many cases in which the syndrome is only partially developed and in which a confirmation of the diagnosis will be welcome The finding of Gamna bodies and the granulo corpuscles in histiocytes in biopsy material will provide some additional evidence but these findings cannot be considered specific It will therefore be necessary to do Frei s test to obtain absolute confirmation of existent or at least recent infection with the specific virus

Frei s test —There are four sources for the antigenic material for this test namely (*a*) aspirated pus from an inguinal or other bubo of a diagnosed case* (*b*) macerated material from an infected gland (*c*) mouse brain emulsion from a cerebrally infected mouse** and (*d*) emulsion of yolk sacs inoculated with the virus The first is probably the most satisfactory but it is very difficult to obtain uncontaminated pus in sufficient quantities and for this reason the mouse brain antigen came into general use some years ago It is acknowledged that this gives less clear cut results and that it is necessary to measure the papules carefully and to compare them with a normal mouse brain control to ensure a satisfactory result (Grace and Suskind 1936) Sulkin (1941) using a yolk sac antigen prepared by Rake McKee and Shaffer (1940) reported more specific results than he obtained with mouse brain antigen A complement fixation test can be done with this same antigenic material this gives a very specific result

The test becomes positive within 14 days of the first appearance of the primary lesion in a very large majority of cases rarely the positive reaction is delayed for another week It usually remains positive as long

* To prepare this antigen pus must be obtained by aspiration from an unopened bubo in a patient who has no other venereal disease This is diluted with four parts of saline heated to 60 C for half-an hour on three consecutive days and tested for sterility by aerobic and anaerobic technique If possible its antigenic properties are tested on a known case of the disease after which it is ready for immediate use but can be kept for some time in the cold A more satisfactory method of preserving the antigen is to freeze the pus and dry it *in vacuo* the powdered pus is dissolved in 50 parts of normal saline when it is required for use

** Commercial preparations are available

as there are lesions and often for some time after they have healed Th test is positive in about 90 per cent of cases of chronic ulcerative elephan tiasis of virus origin

It has been shown that both the intradermal and the complement fixation tests remain positive as long as the virus is present, and, con versely, if the reactions are positive, it is evidence that the virus is stil present This may be as long as 25 years after infection, and it is possibl that such persons are still infectious

Technique—*An intracutaneous injection of 0 1 c cm of antigen* is given into the skin of the arm or leg and at the same time an injection of similar substance that does not contain the specific antigen is given a few inches away The result is read after 48 hours

The result—With Frei's pus antigen, a papule of at least 5 mm in diameter and with either the mouse-brain or the yolk-sac antigen of at least 7 mm consti ... ided by a hyperæmic halo and some- ... The extreme limit of a non-specific ... illy of the order of 1 to 4 mm in

Precaution—Frei (1938) recommends that the test should not be done in the 'peracute' stage or in cases where there is suppuration near the perineum on ac count of the dangers of a generalized or local reaction

This disease may ... when a diagnosis of some o ... taken to exclude the possibil ... s also been established Fre ... gation in venereal clinics

Differential diagnosis—The buboes must be distinguished from other glandular swellings, acute enlargement, *e g* sepsis, chancroid, glandular fever, plague, tularæmia, and malignancy, the elephantiasis and ulcera tion from filariasis and other causes of lymphatic obstruction, from gran uloma venereum, chancroid, cancer, tuberculosis, and actinomycosis, and *the rectal stricture from cancer, syphilis, tuberculosis, ulcerative colitis,* and other dysenteries

PREVENTION

Under this heading it is only possible to make very general remarks In this connectio ... pathia venereum ... ilis for example, i ... obviously preventable by the observation of the simple rules of hygiene Secondly, although, as stated, there is every reason to believe that it is a disease associated with poverty and a lack of hygienic knowledge, its prevalency is not yet fully known, nor whether persons with sub-clinical infections act as carriers Thirdly, it has not received the attention in medical schools it deserves, not even in special classes on venereal diseases Lastly, there is as yet no treatment that can be considered a true specific for the disease

... reporting of the clinically obvious cases of this disease imperative, but clinically obscure cases must be sought out, Frei's-test surveys should be

carried out in certain populations, e g amongst prostitutes, and should be adopted as a routine practice in venereal clinics As satisfactory antigen is now obtainable commercially, this should not present any great difficulty

Much can now be done by **early recognition** and **treatment** of the disease to limit its spread, but if a true specific could be found this line *of attack would obviously be considerably facilitated*

TREATMENT

In view of the diversity of the lesions it is obvious that any adequate discussion on treatment would lead one far beyond the scope of this book *so that it will be necessary to confine remarks mainly to medical treatment*

No true specific treatment has yet been found some promising early reports on the use of certain 'sulpha' drugs were published, but none of these drugs has lived up to this early promise which is not surprising in view of their total lack of success in other virus infections

There is evidence that in the early stages antimony will sometimes cut short the infection The drugs used have been sodium antimony tartrate and Fouadin or its chemical equivalents for dosage *see* GRANULOMA VENEREUM Gold preparations have also been used but as their administration is not without danger and as their specific action in this disease is uncertain it seems unjustifiable to use them

6 grammes daily) continued for several weeks improvement appears to be *effected in a certain number of cases The reversal of a positive Frei s test* is evidence of cure

In rectal stricture considerable improvement in the secondary bowel condition is effected by placing the patient on sulphanilamide three grammes daily for twelve days alone or combined with 3 per cent sulpha drug bowel washes When the inflammatory condition subsides the stricture disappears and it is often possible to avoid any surgical interference

The treatment by increasing doses of Frei s antigen that was advocated at one time was not a great success and has been largely abandoned

Buboes should be treated by local applications of heat infra red rays or hot *fomentations and later when they become soft and fluctuating* they should be aspirated with a sterile syringe and sealed rather than opened and drained

PROGNOSIS

Despite the absence of a truly specific treatment if treatment is under taken early, the prognosis appears to be good This is especially true in the case of men In uncomplicated rectal stricture when the pelvic adnexa are not involved to any extent even when medical treatment has failed something can usually be done surgically In cases in which lymphatic obstruction is already established great care which may be difficult or impossible to maintain, is necessary to prevent ulceration Finally when there is extensive ulceration with fistulæ already formed the condition is hopeless as the unhealthy tissues will not stand up to any plastic operations

of a marriage The explanation for this is that apparently it is only infectious in its early stages In endemic countries it commonly follows circumcision operations, even in children, and other cutting operations such as herniotomy, in the genital area

Social, sex, age and race distribution—More cases are reported in men than in women, but, as in the case of lymphopathia venereum, this may be because the early sores are often inapparent in the woman, who may therefore transmit it to a number of men Children are frequently infected non-venereally

The infection appears to be far more common in the coloured than in the white races, and is confined largely to lower social strata, as is lymphopathia venereum, but there are possibly more exceptions in the case of this disease which suggests that there is some common alternative mode of transmission of infection

ÆTIOLOGY

The Donovan body is *constantly present in the tissues in the earlier* lesions It is a short (1 by 2 microns) 'capsulated' bacillus like body [illegible] is found in large [illegible] *Calymmatobacil*[illegible] *ebsiella inguinale* [illegible] pecificity (so far [illegible] in living tissues, namely in large mononuclear cells, and its suggestive staining reactions, many workers still believe that it is a protozoon or at any rate that it is not a Klebsiella It has also been suggested that the bodies may be cell inclusions and evidence of a virus that is the true causal organism

It is gram-negative, but stains well with Romanowsky stains and for this reason is often given in textbooks as likely to be confused with the 'round' stage of leishmania and with *Histoplasma capsulatum* In the former case, there is very little similarity, but the confusion might well take place in the student's mind, on account of the similarity in the names, the Donovan body and the Leishman Donovan body

The organism has been grown on the yolk sac of the developing chick embryo by Anderson deMonbreun and Goodpasture (1945), who are satisfied that it is a capsulated bacillus

Experimental transmission to man, by rubbing the exudate from a sore on to the scarified skin has been effected

PATHOLOGY

The causal organism appears to be able to enter through the intact or at [illegible] abraded skin or mucous membrane The first lesion [illegible] *possible* that [illegible] organisms The typical cellular reaction is in the corium where [illegible] a round celled infiltration followed by a typical granuloma formation, with the formation of new capillary loops, epithelial cells and fibroblasts There is thinning and later loss of the squamous layer in the central portion of the lesion, while around the edges some epithelial proliferation and down growth of the inter-papillary processes sometimes suggesting squamous celled carcinoma may occur, and at the base of the ulcer true granuloma formation, with no endarteritis, little tendency to necrosis, and no giant-

cell formation However, in the dense fibrous tissue that is found in chronic lesions there may be pin-point abscess formations, as occur in actinomycosis

The ulcer spreads by direct extension, by auto inoculation of ap- [illegible] sfer of infection to more distant [illegible] one direction the other end may [illegible] There is no specific lymph node [illegible] apparently hæmatogenous, has been reported

SYMPTOMATOLOGY

After an incubation period of a few days the **primary sore** appears, usually on the penis or in the groin in men, and on the labia, in the fourchette, or in the vagina in women It is a shallow, indolent and painless ulcer, without any accompanying glandular enlargement It is easily overlooked and in fact few women give any history of a primary sore It usually heals within three or four days, but after a few more days—bringing the total period up to ten days to three weeks from the time of ex- [illegible]

[illegible]

lent lesion These are not clean-cut types and not only are there intermediate types, but one type may develop from the other, usually in the order mentioned If the ulcer is in the groin it usually extends rapidly the full length of the fold of the groin and to the root of the penis and scrotum, and if it is on the penis, it may spread down the penis for an inch or so and then by contact with an apposed surface, *e g* in the groin or on the scrotum cause a new ulcer to develop

The ulcers become secondarily infected, often with a fuso spirochætal infection, and usually emit a foul-smelling sero purulent discharge

In women, the ulcer may spread up the walls of the vagina and involve the cervix Or the lesion may commence as a chronic cervicitis

Transference of infection to other mucous membranes *e g* the mouth, is not uncommon amongst persons with careless and unhygienic habits Rarely, isolated **extra-genital ulcers** are found, which suggest perverted practices

Very extensive areas of skin are sometimes involved In course of time, apparently as an attempt at spontaneous healing fibrotic changes occur at the edges of the ulcer and these sometimes extend into the ulcer, isolating portions of it These fibrous strands subsequently contract, causing considerable deformities, they also interfere with the lymphatic drainage, so that some degree of elephantiasis often occurs, and, in the male, it is not uncommon to see the penis and scrotum involved in a mass of fibrotic tissue and the whole glued to the inner aspect of the thigh, and in women a condition not unlike that of esthiomene may occasionally result

Spontaneous healing of the whole ulcer may occur, but only with extensive scarring Scarring and keloid formation is particularly striking in negroid patients. In the dark-skinned races, the scars are nearly always white and repigmentation seldom occurs

Generalized form.—Recently, a most unusual case in which there were lesions on all parts of the body was seen in New Orleans. Some of the lesions, on the back for example, seemed to preclude direct or indirect external transfer of infection, and suggested dissemination of infection via the blood stream.

To summarize, there may or may not be a primary shallow ulcer,
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DIAGNOSIS

An early diagnosis is very important as treatment in the early stages is much easier and is more effective. A clinical diagnosis can be made with a fair degree of certainty in many cases, by the nature of the bright red velvety lesions which bleed easily and in the early stages are button-like, however, whenever possible the diagnosis should be confirmed by the finding of the specific Donovan bodies in smears from the exudate, from scrapings recovered from the bases or sides of the ulcers, or in biopsy material. This will be easier in the early stages of the infection, as in the late stages the specific organisms become very scanty.

The smear should be stained with Wright's, Leishman's or Giemsa's stain.

The 'Donovan body' has to be distinguished from the round form of leishmania, to which it bears only a very superficial resemblance (*see* p. 143), from histoplasma, from the pneumococcus, which is gram-positive, from the gonococcus, and from Friedlander's bacillus, which also being gram-negative and having a well-developed capsule will present the only real difficulty.

If there is any doubt, a culture on an ordinary agar slant should be made, on this, Friedlander's bacillus will grow, but not, of course, the 'Donovan body'.

A stain which will differentiate the Donovan body from 'other' bacteria, especially of the Klebsiella group, has been suggested by Mortara and Dienst (1943).

Technique.—Make a smear and dry it rapidly in the air or by gentle heat. Stain for two minutes with basic fuchsin (0.5 per cent aqueous solution). Decolorize in 0.5 citric acid solution for approximately five seconds and counter-stain with 1 per cent aniline blue.

Result.—This will stain the intra cellular Donovan bodies a pink colour and the so called capsule a light blue, bacteria will mostly take the blue stain.

Further confirmation can be obtained from the ready response of these lesions to suitable antimony treatment (*vide infra*).

Differential diagnosis.—The condition will have to be differentiated from chancroid (soft sore or Ducrey's infection) by the absence of the characteristic soft glandı ... to intra-dermal dmelcos antigen, ... ous nature of the early lesion, and l ... ndular en-largement, (ii) a positive ... sponse to antisyphilitic treatment, ... bsence of glandular enlargement an ... berculous

and carcinomatous ulceration—by the absence of the characteristic histological pictures in the biopsy material

PREVENTION

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In the
a symptomless carrier state can exist, as is suspected in the former disease, and, secondly, trivalent antimony acts as a specific

TREATMENT

This should be considered under three headings —(i) local, (ii) specific, and (iii) surgical

(i) **Local treatment** —If there is acute inflammation hot magnesium sulphate fomentations should be applied until this subsides The lesions

this application prove too painful, it may be preceded by the application of some anæsthetic ointment (*e g* pantocaine 4 per cent or anæsthesin),

As an alternative to podophyllin, four per cent potassium antimony tartrate (tartar emetic) is used, as before after the preliminary application of some anæsthetic ointment

This local treatment may be applied without any specific treatment, but more rapid cure will be effected if the local and the specific treatment are combined

(ii) **Specific treatment** —Antimony preparations have proven the most successful Many have been advocated but the most successful have been the simple potassium and sodium antimonyl tartrates and the more complex fouadin (pyro-catechin sodium bisulphonate *B P* stibophen) More recently, anthiomaline (lithium antimony thiomalate) has been used with limited success (Robinson and Robinson, 1942)

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e may
be commenced after two to three weeks interval or one of the other antimony preparations may be substituted It is important to continue the treatment for some time after the lesions have healed as they are otherwise liable to relapse

The course and dosage with either sodium or potassium antimonyl tartrate is the same as that given in kala-azar (*see* p 168) Anthiomaline is

given in 2 c cm doses of a 6 per cent solution, from 12 to 15 doses usually being necessary

(iii) **Surgical treatment**—Complete excision of the primary sore or the early secondary lesions is often possible, and should always be considered when an early diagnosis has been made, but partial removal of a large lesion usually leads to infection of the wounds and extension of the process

Again, in the later stages after the specific organism has been destroyed as a result of the specific treatment, there will often be a large [illegible]

the perineum have been destroyed or contractures have taken place plastic surgery will have to be considered

PROGNOSIS

The earlier the treatment is undertaken the better are the chances of a rapid cure With suitable specific treatment the prospects are excellent in early cases and, even in the more extensive ones, provided there are no serious complications and the patient will cooperate cure and repair should eventually [illegible]
for many [illegible]
the life of [illegible]

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SOME COMMON SKIN DISEASES OF THE TROPICS

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Again, in the later stages, after the specific organism has been destroyed as a result of the specific treatment, there will often be a large raw surface left and it may be necessary to scrape or trim the fibrotic edges before the epithelium will begin to grow in from the margins, and, if the [illegible]

PROGNOSIS

The earlier the treatment is undertaken the better are the chances of a rapid cure With suitable specific treatment the prospects are excellent in early cases and even in the more extensive ones provided there are no [illegible]

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SOME COMMON SKIN DISEASES OF THE TROPICS

PITYRIASIS (TINEA) VERSICOLOR

LEUCODERMA OR VITILIGO

Introduction.—There are few true* skin diseases that are confined entirely to the tropics but several are undoubtedly more common more severe and acquire a special significance in tropical climates It is to some of the more important of these that this chapter is devoted Every white sojourner in the tropics will know prickly heat dhobie itch and ringworm of the feet—by their or some other names—as actual afflictions or ever-present dangers Pityriasis versicolor which is a widespread infection amongst natives of the tropics and leucoderma which is a common enough condition in the tropics to justify its inclusion here are more important from an æsthetic than from a morbidity point of view but should be recognized as they may well be confused with other more serious conditions Finally tinea imbricata is perhaps the only skin disease that has an exclusively tropical distribution

These conditions will be discussed mainly from the clinical point of view

PRICKLY HEAT

Prickly heat is probably the commonest of all syndromes suffered by the newly arrived white man in the tropics, and history has recorded that

EPIDEMIOLOGY

It occurs in all tropical and in many sub-tropical countries but is especially associated with the 'green' tropics and with the periods of year when humidity is high, e g the monsoon in India

The dark-skinned native of the tropics rarely suffers from this condition It is far more common in the newly arrived sojourner than in the older residents, but the white man seldom becomes completely immune

most pronounced in the obese

It was more common in the past when the British soldier in India wore heavy broadcloth, when the sojourner wore the formal dress of his country of origin, and when the cholera belt was considered an essential precaution, than it is today when the dress of both the soldier and the civilian sojourner is more rational It occurs more commonly amongst those persons whose circumstances prevent regular bathing and changing of clothes

ÆTIOLOGY AND PATHOLOGY

On the subject of the ætiology of prickly heat, there are several schools of thought

Smith (1927) claimed to have isolated a yeast like fungus, apparently a

The actual cause of the lesions is blocking of the small sweat ducts

Perpetual sweating causes the washing out of the fat from the epithelium, so that these tissues absorb water and become swollen and soft The less completely cornified skin of infants is more readily affected This

swelling leads to occlusion of the openings of the ducts, where the blockage is made complete by desquamated dust on the l[illegible] The damp s[illegible]

poor invasive properties There is already hyperæmia of the skin and the infection causes a slight inflammatory reaction Whenever anything occurs *to increase the skin hyperæmia, sweat* secretion is stimulated and there is tension within the blocked ducts The hair follicles are also involved but to a less extent

Anatomical distribution —It occurs on parts of the body (*a*) where the clothes are held in close contact by pressure, *e g* around the waist under the belt on the shoulders where the weight of the clothes is taken and across the shoulder-blades, (*b*) where there is friction from the clothes, *e g* in the groin, axilla and the backs of the wrists, (*c*) where two skin surfaces are in continuous contact, *e g* under the breasts and between the folds of fat in the obese, and (*d*) on the backs of the hands, a site where the frequent presence of prickly heat cannot be explained on any of the above grounds.

SYMPTOMATOLOGY

The **lesion** consists of red papules and minute clear vesicles with a surrounding red halo, or sometimes on a general hyperæmic background which gives the skin a red granular appearance and a rough, coarse-sand paper-like texture A white powdery desquamation occurs later

Anything that will cause a hyperæmia of the skin, such as exercise a hot bath or a cup of hot tea, will cause an immediate exacerbation of the symptoms, a pricking sensation and intolerable itching

The extremely irritating nature of the lesions causes scratching which will often lead to deeper secondary infection with pyogenic micro organisms and may result in the development of folliculitis, eczema and/or furunculosis

Bromfield (*loc cit*) described the miliarial (as above), the pustular, the pemphigous and the impetigenous types of prickly heat, but it seems more satisfactory to consider these other types, together with multiple *boils which he includes as a fifth type, as complications, for in the* ordinary circumstances in which prickly heat is common they are relatively rare, further, they have causes other than prickly heat though it may be a common one

Ordinarily, prickly heat is a minor annoyance *to the resident in the* tropics but it may dominate the mind of the sufferer, interfere seriously with his sleep and lead him towards neurasthenia, it is more serious in children as not only will it disturb their sleep, but the common complications are more likely to develop in their delicate skins, and in the sick, though it may be easy to control, if neglected prickly heat will often be a serious complicating factor in their illness

PREVENTION AND TREATMENT

It is very much easier to prevent than to cure this condition

The aims of **prevention** are the avoidance of the conditions (*vide supra*) that favour and precipitate the condition —

swelling leads to occlusion of the openings of the ducts, where the blockage is made complete by desquamated duct epithelium The damp surface provides a suitable nidus for micro-organisms of all kinds and the damaged sweat ducts soon *become infected with the common skin-inhabiting micro-*organisms, including monilia, which are mostly of low virulence and have poor invasive properties There is already hyperæmia of the skin and the infection causes a slight inflammatory reaction Whenever anything occurs to increase the skin hyperæmia, sweat secretion is stimulated and there is tension within the blocked ducts The hair follicles are also involved but to a less extent

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a) Avoiding as much as possible the environmental conditions namely high temperature and humidity that produce prickly heat much can be done by the use of air conditioning and the electric fan

b) Avoiding unnecessary exertion unless the immediate removal and change of clothing is possible

c) Avoiding hot baths unless ample time can be allowed for cooling off before redressing

d) Avoiding the taking of long draughts especially of warm tea or coffee when fully dressed

e) Reducing clothing to a minimum and avoiding constrictions around the waist neck wrists etc Children should be allowed to be naked or at most wear a pair of pants and infants should be spared from wearing even a diaper

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g) Bathing and/or taking a shower bath with tepid water at least twice a day

h) Avoiding the too free use of ordinary soap in the bath but washing over with special antiseptic soaps and leaving the lather on to dry with the precaution that sensitivity to such soaps must be carefully tested by each individual

i) Drying the body thoroughly cooling off under an electric fan and finally before putting on the clothes dusting the whole body (except sensitive spots) and especially those areas most liable to prickly heat with an antiseptic dusting powder

j) At night in the absence of air conditioning or an electric fan using a hard mattress with a sheet of grass matting between it and the under sheet a firm pillow and a Dutch wife that is a hard bolster or an open rattan work cylinder over which the legs and arms can be thrown to keep them apart and from lying against the body

k) Keeping a supply of hand towels for mopping the face arms and other exposed parts of the body repeatedly these must be washed and dried frequently

It may be considered that much of this is counsel of perfection but it is by following these practices that many experienced sojourners avoid prickly heat altogether The less fortunately placed must adopt as many of these practices as possible

In addition to the above judicious sun bathing is to be recommended as the tanned skin is not so liable to prickly heat This is particularly true of infants and children

Some observers consider that a reduction of the fat and carbohydrate in the diet with an increase of the protein is of value in reducing liability to prickly heat but the only dietary modification from which the writer has seen direct benefit is the addition of extra salt (2 gramme tablets to each pint of water) This is an important point which should be emphasized The taking of a balanced diet with all the vitamins will of course help to maintain good health and indirectly reduce both prickly heat and more particularly its complications

The aims of **treatment** are much the same as those of prevention It will however usually be necessary to adopt more aggressive tactics

All, or as many as possible of, the above precautions should be observed rigidly After the bath the affected parts must be lathered with antiseptic soap which should be allowed to dry on the skin The tolerance of each person to each soap must be ascertained Some sensitive individuals will be 'burnt' if 'neko' soap, for example, is left on for more than two minutes, so that after this interval it must be sponged off, 15 minutes is usually the time recommended, but in the case of the less sensitive it is unnecessary to wash off the soap at all 'Asepso', 'Afridol' and 'neko' soap are to be recommended The two former being the better

As an alternative to the antiseptic soap and to be applied at other times is a lotion of 1 in 2000 perchloride of mercury in 95% alcohol to be wiped over the affected part after it has been dried, and itself allowed to dry (This will not suit all skins) Then a dusting powder, consisting of camphor—20 parts, menthol—5 parts, boric acid—200 parts, zinc oxide—300 parts made up to 1000 parts with fine talcum powder, should be applied

As an alternative to the mercury spirit lotion and powder, a white lotion made up of zinc oxide 20 per cent, menthol 1 per cent, camphor 2 per cent in 80 per cent alcohol should be dabbed on the affected area with a piece of cotton wool It is usually inadvisable to apply this more than twice during the day At other times an aqueous calamine lotion with phenol will be soothing

As in the case of most skin disease, there is greater danger from over-treatment than from under-treatment, and whenever any treatment appears to be irritating the skin, it must be discontinued and simple aqueous calamine lotion applied

The sulphonamides have no effect on uncomplicated prickly heat, but, for the complications in which pyogenic organisms play a part, sulphathiazole and sulphadiazine will be of considerable value

PROGNOSIS

[illegible]

RINGWORM OF THE FEET (TINEA PEDIS) OR DERMATOPHYTOSIS

This is a worldwide condition but always assumes a much greater importance in the tropics and particularly in the humid tropics In temperate climates, where it is usually known as 'athlete's foot', it often appears in epidemic form in schools and amongst athletic groups whose members transmit the infection to one another in dormitories, changing-rooms and swimming baths, by walking barefooted and by the communal use of bath slippers, sandals and towels In the tropics, where it has innumerable synonyms, *e g*, Hong Kong, Singapore, Bengal, etc, foot-rot (indicating its geographic distribution), mangoe toe, etc, it is endemic

and, where there are native servants walking barefooted, it is practically impossible to avoid infection, even by taking the most rigid precautions

EPIDEMIOLOGY

[illegible]

pavements) than in country districts, amongst men than amongst women, and amongst those who have to do a considerable amount of walking during the day (e g brokers) than amongst those whose occupation is mainly sedentary (e g bankers) The barefooted are usually infected, but the infection is seldom active, and, in any particular set of circumstances, the activity of the condition will usually be in inverse ratio to the ventilating properties of the footwear

ÆTIOLOGY AND PATHOLOGY

The causal organism is a fungus, usually a species of *Trichophyton*, but *Epidermophyton floccosum* and even the monilia, *Candida albicans*, may be responsible, the spores of these fungi are highly resistant and survive on wooden floors, coir or grass mats, carpets, towels, shoes etc , almost indefinitely, despite vigorous treatment with strong antiseptics They are destroyed by autoclaving

These fungi penetrate the epidermis and the superficial layers of the corium only and their toxins cause a serous exudate to accumulate under the epidermis which is thus separated from its source of nutrition and dies

SYMPTOMATOLOGY

The primary site of the infection is often between the fourth and fifth toes it soon spreads to the other interdigital spaces, to the soles, to the dorsum of the feet and particularly of the great toe to the sides of the feet, to the soft area of skin between the ankle and the Achilles tendon, and to the nail-beds The same infection may also spread to other parts of the body (*vide infra*)

Small vesicles appear, they are usually surrounded by a halo of inflammation They are extremely irritatin
between the toes become white and p
exposing the red corium covered by a
which tends to crack, bleeds if damage
infected with pyogenic micro organism
the epidermis gradually resumes its
sodden and separates again Meanwhile, areas of hyperkeratosis develop at the margins of these lesions and form ridges along the edges of the dorsa of the toes and up the interdigital sulci on to the dorsa of the feet The infection will usually spread to the soles, especially to the parts under the arch where the skin is thinnest, here the vesicles in the comparatively thicker epid[illegible]
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PROGNOSIS

This will depend on the personal factor, on the opportunities for applying the measures recommended, and on the vigour and wisdom with which they are applied Seldom, if ever, should it be necessary to invalid patients for uncomplicated prickly heat, but when they persistently develop multiple boils a short period of leave in a cool climate often appears to be the only way to cure this serious complication

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EPIDEMIOLOGY

This disease is at its worst under conditions of high temperature and

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Small vesicles appear they are usually surrounded by a halo of inflammation They are extremely irritating After a few days the whole areas between the toes become white and pieces of sodden epithelium separate exposing the red corium covered by a thin transparent layer of epidermis which tends to crack bleeds if damaged by scratching and readily becomes infected with pyogenic micro organisms After such infection has subsided the epidermis gradually resumes its normal thickness but soon becomes sodden and

arch where the skin is thinnest here the vesicles in the comparatively thicker epidermis cause intolerable itching and develop to the size of a sixpence ($\frac{3}{4}$ inch) or more These blebs contain a clear fluid at first but they often develop into pustules surrounded by areas of inflammation Here too the epidermis may separate in large plaques but it usually flakes off the denuded skin tends to crack and secondary infection and extensive cellulitis may result

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The socks should be of thin cotton material and must be changed at least twice daily, washed immediately in antiseptic lotion and dried thoroughly before being put on again, and boiled periodically After the feet have been washed with lotion or antiseptic soap, the interdigital spaces should be dried by rubbing hard between the toes with a rough dry towel to remove all pieces of loose skin swabbed with spirit and finally powdered with some mild antiseptic powder A useful prescription is

℞ Camphor—2 drachms
sulphur sublimate—½ ounce
zinc oxide—2 drachms
talcum powder—2 ounces

As some individuals are sensitive to sulphur, it may be necessary to omit this from the prescription

TREATMENT

The greatest danger is from overtreatment and for this reason many people are content, without attempting to cure the condition to keep it inactive by the measures advocated above

The patient will usually first come for treatment when the lesions are actually inflamed either as a result of neglect or inexpert overtreatment It is necessary first to reduce the inflammation by hot (as hot as the patient can bear) footbaths of 1 in 1000 mercury perchloride or acriflavin, or boracic or magnesium sulphate fomentations alternating with calamine

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gentian violet 4 per cent in 10 per
let and brilliant green 2 5 grammes
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For complete eradication of the infection the following lotion should be applied twice daily

℞ Salicylic acid—gr xx
Dilute acetic acid—min xxx
Alcohol—95 per cent to the ounce

If there is a sharp local lesion this treatment must be stopped immediately and hot fomentations applied

The socks must be changed twice daily and after a thorough course it will be advisable to discard all old shoes which are almost certainly infected and which cannot be sterilized by any known means

As the nails and nail beds are often a source of re infection special attention must be paid to these They constitute a very difficult problem and often the nail has to be removed and the bed scraped The possibility of complete failure to cure the nail infection must be faced

The ids must be treated by hot footbaths and fomentations and

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Some workers have claimed considerable success in chronic cases with an autogenous vaccine made from the pyogenic secondary invaders which they claim interfere with the action of the fungicidal drugs The local treatment is continued while the vaccine is being given

Complications—The danger of serious cellulitis is very real, but there is another development that provides a good reason for not neglecting these infections, namely, the occasional development of 'ids', trichophytids or dermatophytids, on the other hand, it is believed that these sometimes develop as a result of too active treatment These 'ids' are apparently an *allergic manifestation which result from the patient developing* a sensitivity to the mycotic toxins that have reached the general circulation from the local lesions They take the form of severe erythematous rashes, or papular, vesicular, or pustular eruptions, on any part of the body but characteristically on the soles or palms, the site bears no relation to the initial esion except that in foot infections the 'ids' very commonly appear on he palms, producing a condition known as cheiropompholyx This is a ery distressing condition that completely incapacitates the sufferer for a period of seldom less than six weeks and often for much longer The whole of the skin of the palms separates and secondary infection in some degree s almost inevitable There may be two or three relapses before the condition finally subsides

DIAGNOSIS

A clinical diagnosis is usually sufficient for practical purposes However, it is very easy to confirm that the lesions are due to a fungal infection by taking a scraping from the margin or removing the roof of a vesicle, macerating this in 20 per cent potassium hydroxide solution and examining it under the microscope for fungus hyphæ or spores The main value f the further identification of the fungus which is made by growing it on abouraud's medium is for purposes of prognosis, *Epidermophyton sp* infections are the most amenable to treatment, whereas *Trichophyton rubrum* re the most resistant

PREVENTION

This must be considered under two headings—(*a*) the prevention of nfection and re-infection, and (*b*) the prevention of morbidity, by keeping he conditions at the site of the infection unfavourable to the fungus

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hance of infection and the frequency of re-infection, namely—

(i) By avoiding going barefooted even in one's own bathroom

(ii) By using a bath mat that can be boiled frequently and avoiding one that cannot be so treated

(iii) By using rope or canvas-soled bath slippers that can from time to time be placed in boiling water or cheap grass (raffia) sandals that can be discarded periodically

(iv) When changing outside one's own house by being particularly careful and always using one's own bath mats towels and slippers and avoid bathing pools except those with a very high standard of cleanliness

[illegible] ' the shoes is a most im- [illegible] hoes should be avoided [illegible] dent' shoes in which the [illegible] orated leather shoes, or chaplis', the last named is a form of shoe worn by northern Indians and ade with two leather flaps which overlap one another and are held in ace by a strap and buckle All these types of shoe allow a free circulation of air

The socks should be of thin cotton material and must be changed at least twice daily, washed immediately in antiseptic lotion and dried thoroughly before being put on again and boiled periodically After the feet have been washed with lotion or antiseptic soap the interdigital spaces should be dried by rubbing hard between the toes with a rough dry towel to remove all pieces of loose skin swabbed with spirit and finally powdered with some mild antiseptic powder A useful prescription is

℞ Camphor—2 drachms
sulphur sublimate—½ ounce
zinc oxide—2 drachms
talcum powder—2 ounces

As some individuals are sensitive to sulphur, it may be necessary to omit this from the prescription

TREATMENT

The greatest danger is from overtreatment and for this reason many people are content, without attempting to cure the condition to keep it inactive by the measures advocated above

The patient will usually first come for treatment when the lesions are actually inflamed, either as a result of neglect or inexpert overtreatment It is necessary first to reduce the inflammation by hot (as hot as the patient can bear) footbaths of 1 in 1000 mercury perchloride or acriflavin or boracic or magnesium sulphate fomentations alternating with calamine lotion When the inflammation has subsided after careful removal of all pieces of loose skin with forceps apply gentian violet 4 per cent in 10 per cent alcohol or triple dye (gentian violet and brilliant green 2 5 grammes each and flavine 1 gramme to the litre)

For complete eradication of the infection the following lotion should be applied twice daily

℞ Salicylic acid—gr xx
Dilute acetic acid—min xxx
Alcohol—95 per cent to the ounce

If there is a sharp local lesion this treatment must be stopped immediately and hot fomentations applied

The socks must be changed twice daily and after a thorough course it will be advisable to discard all old shoes which are almost certainly infected and which cannot be sterilized by any known means

As the nails and nail beds are often a source of re infection special attention must be paid to these They constitute a very difficult problem and often the nail has to be removed and the bed scraped The possibility of complete failure to cure the nail infection must be faced

The ids must be treated by hot footbaths and fomentations and mild antiseptic lotions Later the triple dye may be used In a true id' there is no specific mycotic infection at the site and vigorous treatment with strong salicylate preparations for example will usually be disastrous The mycotic infection at its distant focus however may and some workers consider that it should be treated specifically

an s
they
treatment is continued while the vaccine is being given

DHOBIE ITCH OR TINEA CRURIS

The name is derived from the popular tradition (undoubtedly founded on fact) that the *dhobie*, or Indian washerman before returning to their owner the clothes he has taken home to wash, lends or hires them out to his friends, whose mycotic infections are thus widely disseminated

EPIDEMIOLOGY

This is an exceedingly common condition amongst both the native inhabitant and the sojourner in all tropical and many sub tropical countries, and though it does occur in temperate climates especially in epidemic form in schools, it is relatively uncommon

It is very common in the middle-class clothes wearing native of the tropics and occurs, though less frequently, even in those who wear only a loin cloth, amongst sojourners it is not uncommon in the newly arrived and amongst members of the lower social strata, however, the better class native and the experienced sojourner will not usually tolerate the condition, but will take active steps to prevent it

It is more common amongst men than women

It is more common in humid climates but it does not appear to be as dependent on high humidity as are prickly heat and tinea pedis

ÆTIOLOGY

[illegible] or *inguinale* [illegible] also been iso[illegible] the same as [illegible]ve rise to the [illegible]tures of these

SYMPTOMATOLOGY

The two main areas in which this condition develops are, (*a*) the inner aspects of the thighs where radiating from the crutch it passes backwards to the perineum, on to the scrotum and into the anal cleft and (*b*) the axillæ where it spreads out on the lateral aspects of the chest and on the under and inner sides of the arms the former site is by far the commoner The condition is usually bilateral

A red rough scaling area with a raised spreading papular and often pustular margin develops the lesion spreads fan wise It is intolerably *irritating and thus causes continuous and involuntary scratching* even in the sleep which allows secondary infection to occur and increases inflammation The inflammation may be so severe that the patient can scarcely bear to put on his clothes and can walk only with great difficulty

DIAGNOSIS

This can be confirmed by taking scrapings from the margins of the lesions and macerating them in 20 per cent potassium hydroxide as in the case of tinea pedis

PREVENTION

This condition is not nearly so difficult *to prevent as tinea pedis* A good supply of cotton or linen pants and vests should be made available

After removal these should always be washed with soap in hot water

areas should be carefully dried and powdered with talcum powder

TREATMENT

Before treatment is undertaken precautions against re infection must be organized The cotton pants and vests used should be such that they cover the whole affected area that is to say in the case of an axillary in fection vests with at least short sleeves must be used

Though the danger of overtreatment does exist it is usually less in this condition than in tinea pedis one reason being that the areas are more sensitive and the immediate pain of strong applications will prevent their over use When however the areas are actually inflamed strong fungicidal substances must not be applied until the inflammation has been reduced by hot applications alternating with aqueous calamine lotion

Individuals with a tough skin *e g* negroes and some Indians of the labouring class will usually stand strong applications such as formalin (commercial) and liniment of iodine but even in these individuals care must be exercised and the doctor should himself apply the medicaments not leave this to the patient

Perhaps the most useful preparation of all is Whitfield s ointment —

℞ Salicylic acid—gr xxx
Benzoic acid—gr lx
Lanoline—½ ounce
Vaseline—to one ounce

Th

ication half strength
e possible to use the
d to discontinue the
He should also be

warned to apply it to the scrotum very cautiously as it may be exceedingly painful

Alternative applications are 4 per cent gentian violet in 10 per cent alcohol or triple dye There are also several proprietary preparations *e g* Cignolin—a synthetic chrysarobin preparation—in the form of an oint ment or a paint (1 to 3 grains in one ounce of pure acetone) which are useful

Th

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In the case
be made at

A few days of conscientious treatment with any of these applications will usually cure this condition but the treatment must be continued for some time after symptoms have disappeared Refractory cases will occa sionally be encountered in which a succession of medicaments may have to be tried

TOKELAU OR TINEA IMBRICATA

This infection appears to have a purely tropical distribution It has been described in India, Ceylon, Burma, Indo China, Malaya, the Dutch East Indies, Borneo, New Guinea, the South Pacific Islands, and China There are apparently a few foci of infection in Central Africa and in Brazil In India it is encountered almost solely amongst aborigines in South India, Bengal and Assam and in a few plainsfolk who have been in close contact with aborigines

ÆTIOLOGY

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SYMPTOMATOLOGY

The lesion starts as round or oval macules in the centre of which the horny layer of the epithelium cracks and flakes of epithelium begin to separate from within outwards The lesion extends and a larger and larger ring of separating white scales is produced Meanwhile the area in the centre recovers to some extent its normal appearance, but it soon cracks again and a new ring forms within the previous one, so that the lesion eventually consists of a series of concentrically arranged brown (normal skin) and white (separating scales) ri
of rings so that the whole skin area
suggestive of tattooing At the peri
horny layer becomes slightly thickened and raised but there is little inflammatory reaction

The lesions are very irritating

Extensive areas of the skin of the trunk and limbs are involved but the hair is not affected The head palms soles, axillæ and groin are seldom affected

DIAGNOSIS

Clinical diagnosis
of the earlier lesions
simulate ichthyosis bu
found somewhere on the body

PREVENTION AND TREATMENT

Personal cleanliness is an effective preventive measure The disease is said not to occur among persons who anoint their bodies with coconut oil

The lesions themselves respond fairly readily to treatment, but the area involved is so extensive that the whole surface cannot be treated at one time with any of the stronger fungicides An additional complication is the fact that the patients are mostly uneducated aborigines

Most fungicides are effective Castellani's fuchsin paint* is usually recommended Dey and Maplestone (1942), who have had considerable

* This consists of 10 c cm of a saturated alcoholic solution of basic fuchsin in 100 c cm of 5 per cent phenol in water Filter this and add 1 gramme of boric acid After two hours add 5 c cm of acetone and two hours later 10 grammes of resorcinol Keep in dark stoppered bottles

experience with this infection, recommend a paint of one drachm each of resorcinol and glacial acetic acid in one ounce of compound tincture of benzoin

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PITYRIASIS (TINEA) VERSICOLOR

This is such a common infection in Indians of the poorer classes that they are usually quite unconscious of its existence and are often unable to appreciate the fact that their skin is not normal, even when the lesions are pointed out to them It has a wide distribution amongst natives in other tropical countries It is much less common in fair-skinned persons, but does occur, and it is not strictly confined to hot countries though it is much commoner in them

Although this infection is widespread in certain social groups, it is not highly contagious and needs close association before it is transmitted from one person to another

ÆTIOLOGY

It is caused by *Malassezia furfur* The fungus invades the superficial layer of the epithelium and causes a fine scaling There is practically no inflammatory reaction

SYMPTOMATOLOGY

The visible lesions are actually accumulations of fungus on the skin, where they form yellowish or brownish plaques On the brown skin, they appear as a whitish layer of powder, and on the white skin they produce brownish patches As well as the surface lesions there is apparently some change in the underlying pigment, a decrease in the brown skin and an increase in the fair one The lesions commence as small macules the size of a pin's head, they increase in size and coalesce There is a fine powdery desquamation if the affected area is rubbed

The distribution of the lesions is very characteristic It corresponds to an area on which dandruff would naturally fall from the hair, that is to say, over the shoulders, on the front and back of the chest, and on the outer aspects of the arms Sometimes they also appear on the abdomen, neck and face, but seldom on other parts of the body These are not the covered areas, in the class of individual who usually suffers from this condition, as some writers state The distribution seems to suggest that the hair may be an important source of infection

DIAGNOSIS

The condition is readily recognized clinically but confirmation can be obtained easily by taking a scraping from the area macerating it in potassium hydroxide and examining it under the microscope The grape like clusters of spores will be seen

TREATMENT

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ÆTIOLOGY

The causal organism is *Trichophyton concentricum* This micro-organism *differs from others of this group by its apparent inability to* survive saprophytically for any length of time, so that it can only be transmitted by direct contact It penetrates the epidermis, between the epi*dermis and the dermis it multiplies abundantly*, causing the former to separate, and in due course it penetrates the newly formed epidermis and causes further separation

SYMPTOMATOLOGY

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of rings so that the whole skin area [illegible]
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DIAGNOSIS

[illegible] diagnosis is usually easy on account of the unique appearance [illegible] thickened edges will sometimes [illegible]r fresh lesions will usually be found somewhere on the body

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DIAGNOSIS

The condition is readily recognized clinically but confirmation can be obtained easily by taking a scraping from the area macerating it in potassium hydroxide and examining it under the microscope The grape like clusters of spores will be seen

TREATMENT

This presents little difficulty Most fungicides will destroy this superficially situated fungus very easily The commonest application is sodium sulphite 10 to 25 per cent solution This is washed over the affected area after it has been bathed and well scrubbed Or an ointment containing 3 per cent salicylic acid and 6 per cent precipitated sulphur can be rubbed in The hair should be washed also and the sulphite lotion or some other suitable antiseptic applied to it

The condition will usually clear up within a few days but treatment must be continued for several weeks, and all the usual precautions regarding the changing and sterilization of clothes must be taken if relapse and re-infection are to be obviated

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LEUCODERMA OR VITILIGO

Definition—Leucoderma or vitiligo is an acquired condition in which in certain areas there is complete loss of skin pigment, it is characterized clinically by the appearance of ivory-white patches surrounded by an area of normal or increased pigmentation It is neither infectious nor hereditary, though at times it seems to show a familial tendency

EPIDEMIOLOGY

It appears to be much more common in tropical countries, but it occurs throughout the world, in people of all races, all ages and both sexes

ÆTIOLOGY

The cause of leucoderma is not known It is usually classed as a tropho-neurosis In India, it has been observed that in the majority of the cases there is some intestinal infection—protozoal bacterial, or helminthic —*and it has been suggested, on rather slender experimental evidence, that* the condition may be due [illegible] lation of the suprarenals [illegible] and leucoderma are relat[illegible] seldom encountered in the [illegible] dence of hypo-adrenia

PATHOLOGY

Apart from the total absence of pigment, the affected skin is not changed in any way, the activities of the sweat and sebaceous glands are un-influenced, but the hair shafts in the affected area sometimes lose their pigment and become whitish or yellowish in colour

SYMPTOMATOLOGY

The lesions appear as small white macules and extend slowly The margins may remain clear-cut, but in the larger patches they tend to become less sharply defined Sometimes there is an increase of pigment in the adjoining areas, but there is seldom a definite ring of hyperpigmentation around the leucodermic patches

In the well-developed case the lesions can be classified into several types —(*a*) the muco cutaneous type affecting the lips, eyelids and external genitals, (*b*) the pressure type affecting such areas as the waist when there is continuous pressure from clothes, the *dhoti*, the *sari*, or the belt (*c*) the symmetrical type and (*d*) the generalized type, where the white patches fuse to form large lobulated areas and even progress so far that the original skin coloration is completely obliterated

The condition may remain stationary for years but is generally slowly progressive in its course, in exceptional instances the patches disappear spontaneously There are no somatic symptoms associated with this condition but the mental effect of the grotesque disfigurement that may be

produced is often profound The lesions give rise to no subjective symptoms, but the whitened patches are hypersensitive to heat, and tend to become inflamed readily when exposed to the sun

DIFFERENTIAL DIAGNOSIS

The diagnosis does not usually present much difficulty but it is necessary to exclude certain other conditions in which there is complete or partial depigmentation, namely (a) the congenital condition, partial albinism, (b) the bacillary infection, leprosy, (c) the mycotic infection, pityriasis

(ii) atrophic macular

the protozoal infection

onditions of unknown

(*a*) In partial **albinism**, the lesions are congenital there is never any bordering of the depigmented patch by hyper pigmented skin and the patient always has a blue iris

ue to the whitish

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zia furfur can be

(*d* i) In **pinta** which has a limited geographical distribution there is a history of the earlier lesions of this condition which are characteristic and quite unlike leucoderma there is usually a positive Wassermann reaction and possibly some slight response to arsphenamine

(*d* ii) Atrophic macular **syphilide** is a condition where multiple small atrophic areas are found on the trunk and extremities and the atrophy is more marked than the depigmentation

(*d* iii) **Melano leucoderma** generally affects the palms and the soles and rarely the lips it manifests itself by the appearance of patchy leucoderma and melano-

(*f* i) In **morphæ**, the skin shows different grades of depigmentation with smooth, shiny atrophic patches adherent to the underlying tissue

(*f* ii) In **lupus erythematosus** the leucoderma like depigmentation which is pres

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bor

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TREATMENT

This is far from satisfactory and many writers dismiss the condition as incurable However at the Calcutta School of Tropical Medicine over a

period of years the routine procedure indicated below has been worked out, this appears to give satisfactory results in a small percentage of cases (Panja *, 1941, and Panja and Maplestone, 1940)

A **General treatment**—The stools are examined repeatedly for evidence of any intestinal infection, amœbic, bacillary or helminthic If such an infection is found the appropriate course of treatment is given As in addition there is frequently a non-specific bowel disturbance suggestive of excessive fermentation, half to one drachm of liquor hydrargyri perchloridi (*B P*) is given twice daily after meals, in courses of three to four weeks with intervals of one to two weeks, for a period of at least three to six months

B **Diet.**—The patient is advised to avoid food that is likely to cause intestinal fermentation, and to take germinating *gram*, beans and peas which are rich in vegetable protein and yield a good supply of tyrosin, a precursor of melanin

C **Local treatment**—Oil of bouchi (*Psoralia corylifolia*) is rubbed gently on the lesion twice a day for 5 to 10 minutes each time Sometimes the oil produces intense redness, burning and even vesication after a few
rsons the reaction may appear after a
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atches
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the skin has recov [illegible] with
olive oil, either 1 in [illegible] hould
be applied again [illegible] ssible
to use the *oil at all even in higher dilutions*

In young children the diluted oil should be applied from the beginning

To certain tender parts, such as the muco-cutaneous junctions of the lips, eyelids and external genitals, only the diluted oil should be applied

The bouchi oil applications are thought to cause a local stimulation of the melanoblasts, the pigment begins to appear after a time, at first as tiny spots on the margin of the patch or in the regions of the hair follicles from where it may spread to repigment the whole lesion

An alternative procedure is to inject sterilized bouchi oil intradermally into the lesion with a tuberculin syringe and a fine needle, in individual amounts of 0 05 to 0 1 c cm The number of injections will vary with the size of the depigmented patch, small spots of 1 cm or so in diameter only *need a single injection* in the centre, in larger patches the injections are spaced 1 cm or so apart, until the whole area is covered In two to three
[illegible] site of the needle punc-
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ermediate white patches,
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injections are painful so that too many [illegible]
the injection is *sometimes followed* by a small focal ulcer and if several ulcers occur close together they may coalesce and form a relatively large

* This useful paper has been quoted freely in this section

lesion It should however be noted that, apart from the extra discomfort at the time and the subsequent scarring, ulceration does not adversely affect the final result, as the scar usually becomes pigmented

Bouchi oil is an old Indian remedy for the condition, but it seems questionable whether the reaction is a specific one

PROGNOSIS

This is very uncertain, a relatively small percentage of patients show improvement when they persevere with the treatment

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HELMINTHIC INFECTIONS

Introduction—The metazoa that parasitize man differ from man's other parasites, the protozoa, the spirochætes the bacteria and other fungi, the rickettsiæ, and the filtrable viruses, in several important directions Firstly, with few exceptions, they are unable to complete a cycle of development and multiply in a single individual host, or even, except in a very few instances, in one host species, but require one or more intermediate

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less dependent
and acquired
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ucts when dead induce some general and local tissue responses in the host, these are not comparable in their effects to the exo-toxins and endo-toxins, of bacteria for example but helminths, on the other hand, because of their size (all adult helminths are visible to the naked eye) often cause local damage to the tissues, obstruct the normal body functions and deflect the nutrition of the host

Let us consider how these fundamental differences between metazoa and other parasites are reflected in the epidemiology pathology, symptomatology, prevention and treatment of the diseases that are caused by metazoa

EPIDEMIOLOGY

The distribution of most helminthic infections tends to be very limited because the climatic and other local conditions must be suitable not only

for the parasite itself during its exogenous phase, but often for one or more intermediate hosts Also, the complicated life cycle of the parasite is often dependent for its completion on certain special (and, in our Western way of thinking, unusual) habits of the affected population

However, neither of these limitations applies in the cases of the hel-

Trichocephalus trichiurus and *Ascaris lumbricoides* are also cosmopolitan helminths, but are dependent to some extent on suitable exogenous conditions and, therefore, other things (*e g* sanitary conditions) being equal they are more common in humid tropical climates

The helminths that have an encysted stage in some human food substance (*e g* *Clonorchis sinensis*, *Paragonimus westermani*, and the large tapeworms) will naturally be limited to those population groups where the consumption of the particular food substance in which these worms encyst is common and, also, to those persons in the population groups who are in the habit of eating the food raw or insufficiently cooked

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is, however, another habit factor that comes in here—the disposal of excreta Where the practices in this respect are unsatisfactory, as in India where villagers defæcate in the open fields around the village, or in China where human excreta is used as manure, infections by this group, amongst others, are likely to be very prevalent

The filarial group of infections are dependent on certain arthropod intermediate hosts, as well as on favourable climatic conditions for their development with [illegible]
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gans, is very wid
whereas *Onchocerca volvulus*, whose intermediate host is the less common gnat *Simulium damnosum*, is confined within much narrower geographical limits, and *Dracunculus medinensis*, which is dependent for its transmission on a very special set of circumstances regarding drinking-water supply, as well as on the presence of cyclops (and the absence of fish that will prey on them) in the wells, has a very limited distribution, even in countries that are climatically suitable for its transmission

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TABLE XV

Phylum	Class	Sub-class	Order (or group)	Sub-order	Super-family	Genus	Species	
NEMATHELMINTHES	*NEMATODA*		*Aphasmidia*		*Trichinelloidea*	*Trichinella*	*spiralis*	1
						Trichocephalus	*trichiurus*	2
			Phasmidia		*Rhabditoidea*	*Strongyloides*	*stercoralis*	3
					Strongyloidea	*Ancylostoma*	*braziliense*	4
						Ancylostoma	*duodenale*	5
						Necator	*americanus*	6
						Œsophagostomum	*apiostomum*	7
					Trichostrongyloidea	*Trichostrongylus*	*spp*	8
					Oxyuroidea	*Enterobius*	*vermicularis*	9
					Ascaroidea	*Ascaris*	*lumbricoides*	10
					Spiruroidea	*Gnathostoma*	*spinigerum*	11
					Filarioidea	*Wuchereria*	*bancrofti*	12
						Wuchereria	*malayi*	13
						Onchocerca	*volvulus*	14
						Acanthocheilonema	*perstans*	15
						Loa	*loa*	16
						Mansonella	*ozzardi*	17
					Dracunculoidea	*Dracunculus*	*medinensis*	18
PLATYHELMINTHES	*TREMATODA*	*DIGENEA*	*Prosostomata*	*Strigeata*	*Schistosomatoidea*	*Schistosoma*	*hæmatobium*	19
						Schistosoma	*mansoni*	20
						Schistosoma	*japonicum*	21
				Amphistomata	*Paramphistomatoidea*	*Gastrodiscoides*	*hominis*	22
				Distomata	*Fascioloidea*	*Fasciola*	*hepatica*	23
						Fasciolopsis	*buski*	24
					Echinostomatoidea	*Echinostoma*	*spp*	25
					Heterophyoidea	*Heterophyes*	*heterophyes*	26
						Metagonimus	*yokogawai*	27
	CESTODEA	*CESTODA*	*Pseudophyllidea*		*Bothriocephaloidea*	*Diphyllobothrium*	*latum*	31
			Cyclophyllidea	(Super family) *Tænioidea*	(Family) *Tæniidæ*	*Tænia*	*solium*	32
						Tænia	*saginata*	33
						Echinococcus	*granulosus*	34
					Hymenolepididæ	*Hymenolepis*	*nana*	35
						Hymenolepis	*diminuta*	36

vectors is dependent mainly on favourable climatic conditions and is common amongst the densely packed populations in many areas in both India and China Finally, infections that depend on the consumption of raw fish and meat (about one-third of those included in Table XV) are uncommon in India as a large percentage of the population is vegetarian

On the whole, therefore, China provides an infinitely wider field of interest to the helminthologist than does India

PATHOLOGY

The inability of most human helminthic parasites to complete a cycle of development within a single human host means that an helminthic infection is not susceptible to numerical increase within the individual host, and that the weight of the infection, and therefore the extent of the pathogenesis, will usually be dependent on the number of parasites that enter the host, rather than on the tissue reactions of the host, which so often are the determining factors in the production of disease by non metazoal parasites

TABLE XV—Cont

	Intermediate host or hosts	Exogenous free-living habitat	Definitive hosts other than man (Reservoir)	Portal of entry Mouth or Cutaneous	Infective medium	Main sites of pathogenic processes	Temperate Cosmopolitan Warm climate
1	Pig rat, bear	—	Pig rat, bear	M	Pork	G-I tract muscle brain etc	T
2	—	Soil	—	M	Veg *	Lower ileum cæcum	C
3	—	Soil	—	C	Soil	Skin, lungs G-I tract	W
4	—	Soil	Dog	C	Soil	Skin	W
5	—	Soil	—	C	Soil	Skin lungs G I tract	W
6	—	Soil	—	C	Soil	Skin lungs G I tract	W
7	—	?	Monkey	M	?	Cæcum	W
8	—	Soil			Soil	Intestine	W
9	—	—	—	M	Fingers*	Cæcum	C
10	—	Soil	—	M	Food*	Lungs, intestine	C
11	Cyclops & fish	Water	Felines, dog	M	Fish	Skin subcuticle	W
12	Mosquitoes	—	—	C	M bite	Skin lungs lymphatics	W
13	Mosquitoes	—	—	C	M bite	Lymphatics	W
14	Simulium	—	—	C	S-bite	Subcuticle cornea	W
15	Culicoides	—	—	C	C-bite	(Serous cavities)	W
16	Chrysops	—	—	C	C-bite	Subcuticle conjunctiva	W
17	Culicoides	—	—	C	C–bite	(Serous cavities)	W
18	Cyclops	Water	Cattle dog	M	Water	Lung & subcuticle skin	W
19	Snails	Water	—	C	Water	Skin lung liver bladder	W
20	Snails	Water	—	C	Water	Skin lung liver colon	W
21	[illegible]	[illegible]	[illegible]		[illegible]	[illegible]	
22	[illegible]	[illegible]				[illegible]	
23	[illegible]	[illegible]			[illegible]	[illegible]	
24	[illegible]	[illegible]	[illegible]		[illegible]	[illegible]	
25	[illegible]	[illegible]	[illegible]		[illegible]	[illegible]	
26	Snails & fish	Water	Cat dog fox	M	Fish	Small intestine	W
27	Snails & fish	Water	Cat seal pelican	M	Fish	Small intestine	W
28	Snails & fish	Water	Dog cat seal	M	Fish	Liver pancreas	W
29	Snails & fish	Water	Dog cat weasel	M	Fish	Liver	W
30	Snails & crabs	Water	Cat dog pig	M	Crabs	Lung	W
31	Fish & cyclops	Water	Canines felines	M	Fish	G I tract	T
32	Pig	Soil	—	M	Pork*	G I tract muscle brain etc	C
33	Cattle	Soil	—	M	Beef	G I tract	C
34	Man sheep	—	Dog	M	Fingers*	Liver lung brain	C
35	—	—	Rodents	M	Fingers*	Small intestine	C
36	Arthropods	—	Rodents	M	Food	Small intestine	C

* Indicates that the egg is the infective stage

The pathological responses of the host to helminthic infections are usually allergic rather than anti-toxic in nature

SYMPTOMATOLOGY

In the majority of helminthic infections, the presence of only a few parasites will not cause pathological lesions of sufficient importance to produce clinical evidence of infections, so that in circumstances of low endemicity the vast majority of the helminthic infections will be symptomless It is only when the initial invasion is exceptionally heavy or when the individual is subjected to repeated invasions that these infections reach the clinical threshold, and it is even less frequently that the diseases caused by helminths reach an acute stage Another result of this poorhost tissue response is seen in the long duration of most helminthic infections

PREVENTION

The complex life cycles of most helminths apparently display several Achilles heels, but in practice it is found that these points are not usually as vulnerable as one would at first suppose, because of ingrained customs *of the affected population groups To take some examples from the infections mentioned above,* hookworm infection could be obviated by proper *sanitary disposal of fæces or by the use of proper footwear, clonorchiasis* and tæniasis by the avoidance of undercooked fish and meat, dracontiasis by keeping wells covered *or* by drinking only filtered or boiled water, and *filariasis by avoiding mosquito bites But in each case it will be many* decades and in some cases probably centuries before it will be possible to impress on the population groups most affected, the necessity for altering their habits to fulfill these apparently simple requirements This estab
[illegible] of preventive proce-
than in the case of

TREATMENT

In the treatment of bacterial and other infections we usually have to rely largely on the host-tissue reaction and are *often content to stimulate* or bolster these rather than to attempt direct action against the parasite In helminthic infections, however, the relative poverty of the host-tissue
response comp [illegible] neces-
sary to use dr [illegible] ize it
In the case of [illegible] with
the blood parasites it is more difficult though some progress [illegible] been achieved, but with the lymph and tissue parasites it presents a problem that has in no case yet been satisfactorily solved

CLASSIFICATION

Some form of classification of helminthic diseases is desirable, at least as a concession to the scientists' natural desire for order, if not as an aid to memory for the student Classification might be along several lines, some of these will be considered —

I *Classification according to the taxonomic relations of the causal*
[illegible] 588 and 589

saginata and *Echinococcus granulosus* It is felt, however, that this table which gives an outline of the taxonomy of the majority of the human helminths (some of which are not deemed of sufficient importance to need further consideration in this book) may be of value for reference when the names of classes, subclasses, orders sub-orders and super-families are mentioned by other writers It will also save the necessity for any further reference here to the subject of taxonomy

II ***Classification according to the medium of transmission and mode of entry of the causal parasite*** —In this classification five groups can be considered

[illegible] contaminated fingers [illegible]d food This would [illegible] not a common source [illegible] tend to sink rapidly, so that any primitive form of sedimentation or filtration will remove them

(ii) Oral infection through raw food substances that contain encysted larvæ

(iii) Oral infection with water containing infected crustaceæ

(iv) Cutaneous infection by active entry of the pre-adult forms (larvæ or cercariæ) from water In several instances the entry may also occur through the mucous membranes of the buccal cavity or pharynx but in no case is this the important route of infection

(v) Cutaneous infection by entry of larval forms conveyed by arthropods

The arrangement of the important helminths according to this classification is shown in the table below —

TABLE XVI

Showing Helminthic Parasites Arranged according to their Portal of Entry and the Medium of Transmission

Portal of entry	*Medium of transmission*	*Species*	
Oral	Fingers and contaminated food	*Trichuris trichiura*	*Enterobius vermicularis*
		Ascaris lumbricoides	*Trichostrongylus spp*
		Œsophagostomum apiostomum	
		Hymenolepis nana	*Hymenolepis diminuta*
		Echinococcus granulosus	
	Special food substances containing encysted larvæ	*Trichinella spiralis*	*Gnathostoma spinigerum*
		Fasciola hepatica	*Fasciolopsis buski*
		Echinostoma spp	*Heterophyes heterophyes*
		Metagonimus yokogawai	*Opisthorchis felineus*
		Clonorchis sinensis	*Paragonimus westermani*
		Tænia solium	*Tænia saginata*
		Diphyllobothrium latum	*Gastrodiscoides hominis*
	Water containing infected crustaceæ	*Dracunculus medinensis*	
Cutaneous	Active invasion by larvæ or cercariæ from soil or water	*Strongyloides stercoralis*	*Ancylostoma duodenale*
		Ancylostoma braziliense	*Necator americanus*
		Schistosoma hæmatobium	*Schistosoma mansoni*
		Schistosoma japonicum	
	Invasion by larvæ conveyed by arthropods	*Wuchereria bancrofti*	*Wuchereria malayi*
		Acanthocheilonema perstans	*Loa loa*
		Onchocerca volvulus	*Mansonella ozzardi*

III *Classification according to the parasitological findings.*—This is shown in tabular form below —

TABLE XVII

Showing Helminth Infections Arranged According to the Clinical Parasitic Findings
A Diagnostic Classification

Stage	Material	Species	
ggs	(i) In fæces		
	(a) Constant, in large numbers	*Trichuris trichiura*	*Ascaris lumbricoides*
		Ancylostoma duodenale	*Trichostrongylus spp*
		Necator americanus	*Fasciolopsis buski*
	(b) Periodic or scanty	*Schistosoma mansoni*	*Schistosoma japonicum*
		Gastrodiscoides hominis	*Fasciola hepatica*
		Heterophyes heterophyes	*Echinostoma spp*
		Opisthorchis felineus	*Metagonimus yokogawai*
		Clonorchis sinensis	*Œsophagostomum*
		Diphyllobothrium latum	
		Hymenolepsis nana	*Hymenolepis diminuta*
	(c) Rare	[*Schistosoma hæmatobium*]	[*Enterobius vermicularis*]
		[*Paragonimus westermani*]	
		[*Tænia solium*]	[*Tænia saginata*]
	(ii) In a perianal swab	*Enterobius vermicularis*	
	(iii) In the urine	*Schistosoma hæmatobium*	
	(iv) In the sputum	*Paragonimus westermani*	
arvæ	(i) Fæces	*Strongyloides stercoralis*	[*Ancylostoma duodenale*]
		[*Trichinella spiralis*]	[*Necator americanus*]
	(ii) Blood	*Wuchereria bancrofti*	*Wuchereria malayi*
		Acanthocheilonema perstans	*Loa loa*
		Mansonella ozzardi	
	(iii) Discharge from ulcers	*Dracunculus medinensis*	
	(iv) In subcutaneous tissues, or muscle	*Onchocerca volvulus*	
		Trichinella spiralis	
	(v) In cysts	*Echinococcus granulosus*	
dult vorms r roglottids	(i) In fæces	*Tænia solium*	*Tænia saginata*
		[*Diphyllobothrium latum*]	
	(ii) In subcutaneous tissues	*Gnathostoma spinigerium*	
		[*Loa loa*]	
		[*Onchocerca volvulus*]	

Note The brackets indicate that the species also appears under another heading hat is more important from a practical diagnostic point of view

Other classifications that might be adopted would be

IV *According to the nature of the intermediate host or hosts, of the definitive hosts other than man, and/or of the habitat of the free-living phase,*

V *According to whether they are infections of warm, or of temperate countries, or are cosmopolitan in their distribution,*

VI *According to the main sites of the pathological processes that they engender*

There is little to be gained by regrouping the worms according to th
last three classifications but in the second half of Table XV these data
tabulated

None of the above classifications would appear to be entirely sa
factory for the purpose of this book, but the following modification of (
the pathological classification, seems to allow a consecutive presenta
of the subject and has therefore been adopted here

CLASSIFICATION ADOPTED

A. Intestinal parasites—These can be divided into several groups

(i) Nematode worms whose portal of entry is the mouth, whose
fective stage is the egg, whose cycle is a relatively simple one and does
include an intermediate host, and whose distribution is cosmopolitan
this group are included *Trichuris trichiura*, *Enterobius vermicularis*
Ascaris lumbricoides, and they are described under the general head
'Cosmopolitan intestinal nematode infections'

(ii) Nematode worms whose usual portal of entry is through the sk
whose infective stage is the filariform larva, whose life cycle, though
does not include an intermediate host, requires special exogenous con
tions and whose distribution is mainly tropical In this group are inclu
Ancylostoma duodenale *Ancylostoma braziliense* *Necator americar*
Strongyloides stercoralis, and *Trichostrongylus spp*, though the usual po
of entry of the last named is not known, it is apparently capable of
tering through the skin or the mouth They are described under
heading 'Tropical intestinal nematode infections'

(iii) The tapeworms, *Diphyllobothrium latum* *Tænia solium*, *Tæ*
saginata, *Hymenolepis nana* and *Hymenolepis diminuta* which are no
very homogeneous group in their life cycles, though their portal of en
is in each instance the mouth, and except in the case of *H nana*, th
enter in the larval stages, they are cosmopolitan in their distribution Th
are described under the heading Tapeworm infections'

(iv) *Trichinella spiralis* which must be considered here because
adult stage is in the intestinal mucosa and produces intestinal sympto
though the larval stage causes more serious symptoms in the same in
vidual host Infection is by ingestion of the encysted larval stage in me
it is an infection of temperate zones This is described under the head
'Trichinosis'

(v) The intestinal trematodes, of which only one *Fasciolopsis bus*
is described here These worms have a complex life cycle they usua
enter their determinative hosts in their larval stage and are tropical
their distribution (*Fasciolopsis buski* will be described more appropriat
with the other flukes)

B Parasites of lymphatics, subcutaneous tissues and serous cavit
—These can be divided into three groups —

(i) The filariae, Wuchereria bancrofti *Wuchereria malayi*, *Onch*
loa and *Mansonella*
age by the agency of
described under the hea

(ii) The guinea worm, *Dracunculus medinensis*, which gains entry

ASCARIASIS

EPIDEMIOLOGY

This is a cosmopolitan infection, but, because the climatic conditions in tropical countries are more favourable than those of temperate and cold countries to the exogenous phase of this worm, and, because on the whole the populations of the former adopt a lower standard of both personal and environmental hygiene, the infection is a widespread and heavy one amongst the inhabitants of most tropical countries

Ascariasis is a good indicator of the sanitary advancement in any population, and in temperate countries it is confined mainly to insanitary population groups and is particularly prevalent amongst poorer class children

ÆTIOLOGY

The causal organism —*Ascaris lumbricoides* is the only species of the genus which infects man *Ascaris suum* of the pig is morphologically identical, but physiologically distinct and mutual interchange of hosts apparently does not occur

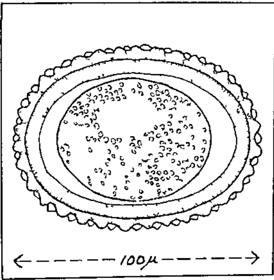


Figure 142 The fertile egg of *Ascaris lumbricoides*

The **egg** is the infective stage The fertile egg which measures 45 to 75 microns by 35 to 50 microns, has a thick but transparent coarsely mammilated albuminoid shell, it is unsegmented and it contains an almost globular protoplasmic mass of moderate sized regular granules

The **larvæ** develop inside the egg and pass through two stages before they emerge The larva that eventually emerges from the egg is 0 2 to 0 3 millimetres in length by 0 014 mm in diameter, it passes through two more developmental stages and increases to 1 to 2 millimetres in length

The **adult** is a large round worm, the male is 15 to 31 mm by 2 to 4 mm in diameter and the female 20 to 35 by 3 to 6 mm but is occasionally longer

The life cycle —Mature (embryonated) eggs are ingested in the duodenum the shells split and active embryos emerge these penetrate the mucous membrane of the intestine and enter a lymphatic vessel or venule*

* There is experimental evidence for this (Ransom and Cram 1921) If however the larvæ (about 14 microns in diameter) travel *via* the venules they will have to
pass through the liver whereas if they trav
liver There is no evidence of any damage
is considerable It is possible that this is
development in the latter organ or it may
lymphatics and miss the liver

to reach the right side of the heart and the lungs in the blood stream, in the lungs the larvae moult twice during a sojourn of several days, and eventually they penetrate into an alveolus whence they migrate up the trachea and down the œsophagus to reach the intestine once more and become adults In their larval stages they live on blood, but the adults are almost entirely lumen feeders The female lays eggs at the rate of nearly a quarter of a million a day, these are passed out with the stools, and mature in the soil The adult worms may live for at least 15 months

Conditions favouring transmission—A moderately high temperature

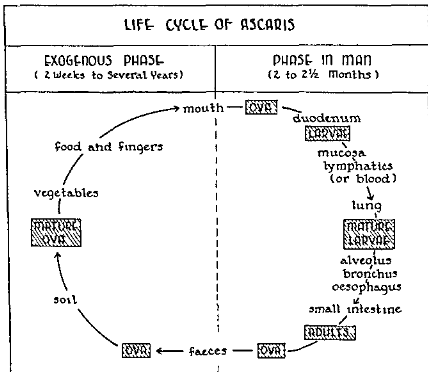


Figure 143

(80° F) favours the exogenous phase of the worm and though the eggs will survive drying and may be blown about in dust they reach maturity earlier in a warm humid environment

The infection is acquired from the fæces contaminated ground by means of soiled hands and other objects that children frequently place in their mouths, contaminated food particularly vegetables in the growing of which human excreta have been used as manure and from contaminated water supplies

PATHOLOGY

This is not as clear-cut as in many other helminthic infections

The migrating larvæ during their sojourn in the lungs damage the capillaries and cause a cellular, largely eosinophilic, reaction, there is des-

quamation of the alveolar epithelium, bleeding into the alveoli, and often in heavy infections a pneumonitis or a true pneumonia resulting from secondary bacterial infection

Blood-stained sputum containing ascaris larvae may be coughed up

Aberrantly migrating *larvæ may produce thrombotic* lesions in various organs, including the brain and the cord, but such instances are rare

The **adults** in the intestinal canal do not cause any gross pathological lesion as a rule, but *when the infection is very heavy*, they may wander into other organs, *e g* the gall-bladder, liver, bronchus, or even eustachian tube, and produce considerable local disturbances, or in the intestine itself, they may become impacted causing obstruction, directly or as a result of intussusception, and even perforation They also produce a 'toxin', apparently an albumose with neurotoxic, anaphylactic, anti-peptic, and other properties, especially after they are dead, that causes a local reaction in the bowel, and is absorbed, producing a 'toxæmia' that may be fatal in ill-nourished children

The writer has removed half a bucketful of worms from the intestinal tract of a patient who died of intestinal obstruction, they were aggregated in solid knots in different parts of the intestinal tract There were certainly a thousand round worms, but the record is apparently held by Ryrie who counted 1488 from one patient.

Blood picture—There is usually an eosinophilia, often up to 1,500 (or 20 per cent) per c mm, but the degree of eosinophilia is no indication of the weight of the infection

SYMPTOMATOLOGY

The symptoms produced are very variable in degree and very protean in character *In the majority of light infections, there are probably* no symptoms due to the ascaris, but some observers believe that in children even these light infections frequently cause intellectual retardation, stunted growth, and general sub-health

In heavy infections, during the stage of migration the larvæ may undoubtedly cause pneumonitis and pneumonia, and more rarely the conditions that result from embolism in the various organs and tissues referred to above

During their intestinal phase, the adults cause vague abdominal pains indigestion nausea and vomiting, malnutrition, pallor (not necessarily associated with anæmia) and heavy rings under the eyes, restlessness and insomnia and, in infants, convulsions and death, as well as the symptoms produced by the worms when they wander into other organs, *e g* suffocation when they obstruct the bronchi, and peritonitis when they cause intussusception appendicitis, or perforation

Children are very likely to pass live worms in their stools, or these may escape *per anum* between stools, or be vomited, or escape through the nares, the incident causes considerable alarm to the patient, or the parent, but is not in itself of any special significance beyond indicating the presence of the worms and the probability that there are more

DIAGNOSIS

The diagnosis does not ordinarily present any difficulty, as the female passes large numbers of eggs regularly throughout her life, and these can

be readily recognized, though it may be necessary to employ a concentration method Ascaris eggs are not well demonstrated by floatation methods It is said that a certain percentage of persons, less than 4 per cent, will harbour male worms only, in such cases there will be no ova and a diagnosis will be best made by the therapeutic test

The characteristic ascaris egg has been described above, but occa-

PREVENTION

All-round sanitary improvement will be necessary to prevent or reduce this infection It will however be advisable to find out which are the most highly infected groups in a population, and then what is the main source of infection, so that special measures may be adopted It is often a homestead problem in which the infection is maintained by promiscuous defæcation of children, and until this has been corrected the infection will be certain to recur Education, especially in schools, will be an important means of achieving this

Mass treatment, in which it will be most essential that all children are included, will effect some improvement by reducing the source of infection, but, unless combined with other sanitary measures, it will not produce any permanent reduction in infection in the population

TREATMENT

Santonin, which was at one time looked upon as a specific has little to recommend it, and has now been replaced by other safer and more efficient drugs

Oil of chenopodium (B P) is very effective but is best given with tetrachlorethylene, 1 c cm of the former with 3 c cm of the latter for an adult and for children 0 25 c cm of this mixture for every year of *apparent* age This should be given shaken up with an ounce of saturated sodium sulphate solution

For the safety of the patient it is essential to reduce the dose of oil of chenopodium, as indicated above, in the case of children, but since the worms are the same size whatever the size of the host, the smaller doses may prove inadequate (Maplestone and Mukerji 1938) For this reason, the less toxic hexylresorcinol may be substituted in the case of young children

Hexylresorcinol is at present available only in the form of the proprietary caprokol crystaloids (Sharpe and Dohme) containing 0 1 gramme or 0 2 gramme each This is given on an empty stomach (5 hours after food) in doses of 1 gramme (5 x 0 2 g) for adults and older children 0 8 gramme for children between 6 and 11 years, and 0 6 gramme for children from 1 to 5 years of age This dose is followed in two hours by an ounce of saturated sodium sulphate solution (for an adult and less for children)

In the case of either drug if a good reaction is not secured within a few hours the purgative should be repeated, as the early removal of both the drug *and* the dead worms is very desirable, there is evidence that a toxin may be absorbed from the disintegrating ascaris

The full dose of the former medicine will usually cure 90 per cent of adults, but with the smaller dosage in children the cure rate is not so high For the latter drug, an all-round 90 per cent cure rate is claimed

THREADWORM (PIN-WORM) INFECTION OR OXYURIASIS

EPIDEMIOLOGY

This infection is world-wide, it is also probably both the commonest and the most harmless of intestinal helminthic infections It has been shown to be present in 35 per cent of a general population group in Washington (D C, U S A) and in nearly 70 per cent in certain children's institutions Writers usually assume that it will be more common in the tropics, on account of the lower sanitary standards in these countries, but this is by no means a foregone conclusion, as the habits and general mode of life of many inhabitants of the tropics are such that they would be less likely to foster this infection than are those of the natives of more advanced western countries However, few reliable figures are available

As well as being an institutional disease, it is a family disease The highest infection rate will always be found in the children

ÆTIOLOGY

The causal parasite, *Enterobius vermicularis* (previously placed in the genus *Oxyuris*, hence the name 'oxyuriasis'), is a very small thread-like nematode worm, the male, which is seldom seen, is 2 to 5 millimetres long by 0 1 to 0 2 mm in diameter and the female, which has a fine pointed tail, is 8 to 12 mm long by 0 3 to 0 5 mm in diameter The eggs are 50 to 60 microns long by 20 to 30 in diameter, they are ovoid in shape with one side slightly flattened, they have a moderately thick transparent shell, and when seen usually contain a fully-developed embryo

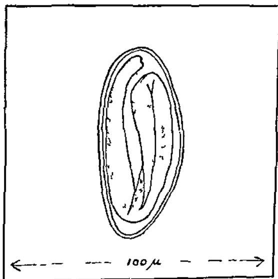


Figure 144 The egg of *Enterobius vermicularis*

Their **life cycle** is a simple one The eggs are swallowed, larvæ hatch out in the duodenum and pass down the intestinal canal to the cæcum, moulting twice *en route*, here they develop into adults, they attach themselves to the mucosa of the cæcum and large intestine, but to ovipost the females migrate outside the intestinal canal The eggs remain attached to the skin in the grooves around the anus, to the host's clothes, or to the bedclothes, or they fall to the ground where when dry they be

come part of the dust of the room and in an infected household can be recovered in large numbers from the dust lying on furniture or even along the tops of pictures on the wall The host may reinfect himself by scratching the skin around the anus or the eggs may regain entry into the same host or into other members of the family in innumerable ways and the cycle will commence again

The cycle takes about two months to complete

PATHOLOGY AND SYMPTOMATOLOGY

It is quite obvious that in the large majority of infected persons there is no pathogenesis There is no very convincing evidence that the worm

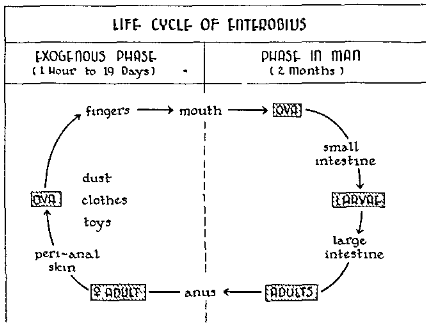


Figure 145

produces any lesions in the intestinal tract catarrhal inflammation mucosal erosions and allergic manifestations in sensitive persons are referred to Acute and subacute appendicitis are sometimes mentioned in 'the
orms are found in 5 per cent of
hird showed acute inflammation
a population with possibly a 35
very convincing evidence of the
predilection for this site

The female worm however causes anal pruritus which leads to scratching and trauma with the attendant dangers of secondary infection This will lead to disturbed sleep and irritability and may thus indirectly affect the health of a child

There is a little evidence that in heavy infections in ill nourished children some invasion of the mucosa may take place with resultant diar

rhœal and other disturbances, but with this possible exception it seems very doubtful if any of the varied symptomatology that is popularly attributed to this worm is really caused by it

DIAGNOSIS

Eggs will not be found in the stools of more than about 5 per cent of infected persons, so that stool examination is useless To find the eggs it is necessary to take a swab from around the external anal orifice The best method of doing this is with the NIH (National Institute of Health) swab



Figure 146 NIH swab (Hall 1937)

The NIH ... the end ... inch sq ... band ... venienc ... test tube with the other end of the glass rod passed through the cork with which the test tube is closed The cellophane swab is wiped

and a coverslip is applied Under the low power the slide is examined and eggs will be seen lying between the slide and the cellophane and adhering to the latter

PREVENTION

The main source of infection lies in the patients themselves and the other members of the household and in their immediate environment Prevention therefore consists in simultaneous and thorough treatment of every member of a household, combined with a very complete cleaning of the house and the maintenance of a high standard of personal cleanliness Such measures as providing night clothes that prevent children scratching their anal orifices and transferring

certain to tak
not be solved

TREATMENT

The most satisfactory results are obtained with gentian violet, the dosage is the same as that for strongyloidiasis (see p 632), but it is usual to divide the course into two 8 day periods, leaving an interval of one week between courses (Wright & Brady, 1938) Hexylresorcinol is also very effective, especially if the oral administration (for dosage see ASCARIASIS) is combined with an enema of a 1 in 1,000 dilution of the same drug After the n
is given and the b
enema of one pint
long as possible
ation, a warm-water bowel wash should be given

If the above drugs are not available, tetrachlorethylene, as given in hookworm infection (see p 626), will be found relatively satisfactory

Whatever drug is used in order to test cure peri anal swabs should be taken It is unsafe to assume that the patient is cured until seven such swabs (preferably NIH) have been negative

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WHIPWORM OR TRICHURIS INFECTION

EPIDEMIOLOGY

This infection is again world wide but it is probably more common in *the tropics especially the humid tropics It is epidemiologically closely* associated with ascaris infection but it is not so widespread and is less prevalent in dry areas It is more common amongst children than adults

ÆTIOLOGY

The causal parasite *Trichuris trichiura* (or *Trichocephalus trichiurus*) measures from 3 to 5 centimetres the male being slightly smaller than the female It is a whitish grey worm with a filamentous anterior three fifths and a stouter posterior two fifths this gives it its very appropriate name The **egg** measures about 52 by 22 microns it has a double shell the outer one of which is bile stained it is lemon shaped and at each pole there is a hole through the shell that is filled with a non staining substance which like the bung in a barrel projects slightly to make button like prominences at each end

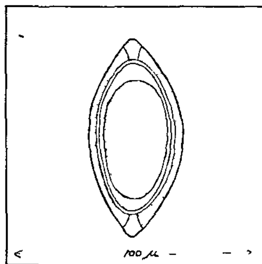


Figure 147 The egg of *Trichuris trichiura*

The **life cycle** is as follows —Fully embryonated eggs are ingested by man who is the only host and

tance just under the surface in a way that prevents easy mechanical removal Here the females produce their immature eggs which pass out with

The developmental phase from egg to

After about two weeks under optimal

They are now ready for ingestion but

about a year and when they are ingested the cycle starts again

PATHOLOGY AND SYMPTOMATOLOGY

These worms appear to produce distinctly more damage in the intestines than do thread worms, and it is also believed that they suck blood They are occasionally associated with a moderate eosinophilia which suggest the absorption by the host of some allergin, and insomnia, loss of appetite, and 'nervousness' are attributed to them, even when infections are light, but there is better evidence with regard to heavy infections, and it is believed that quite severe anæmia, diarrhœa, emaciation, and a condition somewhat similar to that produced by hookworm infection may occur

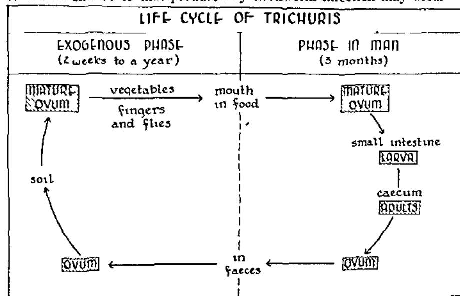


Figure 148

DIAGNOSIS

easily in the te the search are a rough indication of the degree of infection

PREVENTION

There are no special measures to be recommended This infection, like that of ascaris, is a good indication of personal and environmental hygienic practices of a community

TREATMENT

There is no specific, available for general use, for the treatment of this infection All the anthelminthics mentioned above should be tried It is usually found that heavy infections are reduced by tetrachlorethylene and *oil of chenopodii* nfections ugs are often uninflu irge will be better if and then a high alkaline enema

There is however one substance that is apparently a specific, namely, leche de higueron, which is the sap of certain species of the genus *Ficus*

Ficus glabrata and *F doliaria* grow in Central and South America where they are used extensively as anthelminthics The latex contains a proteolytic ferment, but this can only be preserved under conditions of refrigeration, and it is not yet commercially available outside the countries where it grows (Faust, D'Antoni and Sawitz, 1943) In several countries, *e g* India, attempts have been made to use for this purpose the latex of the local species of *Ficus*, but so far without success The fresh latex is given in a two-ounce dose on an empty stomach, preferably at night, after thorough cleansing of the bowel by salines and enemata

The cure is tested by examination of the stools for ova 3 to 5 days after treatment If they are still present, the treatment should be repeated after a week's interval

REFERENCES

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PATHOLOGY AND SYMPTOMATOLOGY

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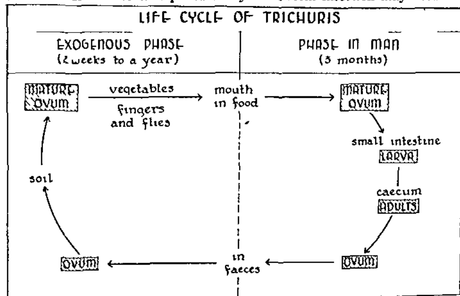


Figure 148

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PATHOLOGY AND SYMPTOMATOLOGY

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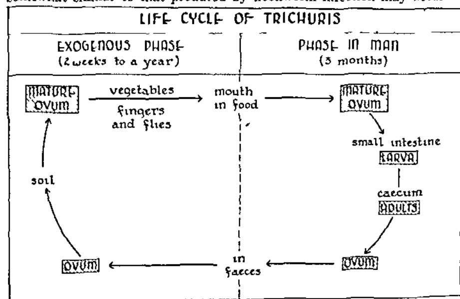


Figure 148

DIAGNOSIS

This presents no difficultie ... the fæces and are unmistakable ... arch when the infection is light T ... ough indication of the degree of infection

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TROPICAL INTESTINAL NEMATODE INFECTIONS

ANCYLOSTOMIASIS AND HOOKWORM DISEASE

ANCYLOSTOMIASIS AND HOOKWORM DISEASE

Definition.—Ancylostomiasis or hookworm infection, that is infection by *Ancylostoma duodenale*, *Necator americanus*, or *Ancylostoma braziliense* may be symptomless or, if the infection is a very heavy one and/or the subject is undernourished or otherwise particularly susceptible, it may give rise to symptoms of various degrees of severity. The most prominent of these are skin eruptions at the point of entry or along the route of the migrations of the larvae—conditions known respectively as water

(or ground) itch' and 'creeping eruption'—and, when the worms are established in the bowel, anæmia, cardiac dysfunction, gastro-intestinal disturbances, and debility—a symptom complex known as hookworm disease The infection is transmitted from man to man by faecal contamination of the so l and . . . [illegible] . . . worms through the skin usually of the . . . [illegible] . . . n warm climates, and occurs in tem- . . . [illegible] . . . temperature conditions approximate . . . [illegible] . . . climates

Historical.—There are very early authentic records of the existence of hookworm disease, *e g* in the Ebers Papyrus and unmistakable clinical examples can be traced in the medical writings throughout the ages up to the middle of the 19th century, but the real nature of the disease was not realized prior to 1853 when Bilharz definitely associated 'Egyptian chlorosis' with the presence of the worm described ten years previously by Dubini in Italy and named *Agchylostoma duodenale*

Wucherer confirmed these observations in Brazil in 1866 where he associated the worm infection with 'tropical anæmia' Surprisingly, it was another twenty years before Grassi and the brothers Parona showed that the condition could be diagnosed by finding the ova in the stools

The first serious medical attention was attracted to the disease by the St Gothard tunnel outbreak in 1880 When this tunnel was completed in 1882, the workers were dispersed and many were employed . . . [illegible] Europe where they disseminate [illegible] ognized in the tin mines in [illegible] recorded in tropical countries [illegible] other parasites, as it frequently is even today

It was first . . . [illegible] . . . the infection had undoubtedly be[illegible] the infection was almost en tir[illegible] orm in tropical Africa first des[illegible]

In 1893, Looss discovered that the ordinary route of infection was not as had been previously supposed, by the mouth from contaminated food or fingers but through the skin, usually of the feet, whence the larvæ migrated *via* the lymph channels blood stream lungs œsophagus and stomach to the duodenum and small intestines His epoch making monograph on this subject was published in 1911

Geographical distribution.—Hookworm infection occurs in practically all humid tropical countries and in a number of subtropical areas in both the northern and the southern hemispheres Several outbreaks have been reported in temperate countries in mines and tunnels, where the temperature and humidity conditions simulate those prevalent in tropical countries

It occurs in the southern states of North **America,** throughout Central America, and in South America—in Venezuela, the Guianas, Brazil, Paraguay, Uruguay, and Argentina—as far south as Buenos Aires, but not in the countries on the west coast It occurs throughout the west coast of tropical **Africa,** on the east coast in Tanganyika and Portuguese East Africa and in Madagascar *Necator americanus* is the only important human hookworm in all these countries, except for a few areas in southern Brazil, in Paraguay, in Panama, and in Portuguese West Africa, where, although the infection is predominently *Necator americanus, Ancylostoma duodenale* occurs also

Ancylostoma duodenale is solely responsible for the infections in Egypt, in North Africa, especially Tunisia, in southern Italy and Sicily, and in the mines in Spain and countries in **Europe** where the infection still persists

In **Asia,** infection is widespread in India, southern China, Burma, Siam, Indo-China, Malaya, the Dutch East Indies and Japan, Borneo,

ie Philippines, and New Guinea, and in Queensland in **Australia.** In most of these areas both species are found

In **India,** there are few areas throughout the plains free from the infection, but in very few places does it assume serious proportions Some of the coastal areas in southern India and Ceylon are exceptions, here the infections are almost solely *Necator americanus,* and in Ceylon in particular it has been a very serious public health problem In northern India, the infection is mainly *Ancylostoma duodenale* and in the central portion of the country and in the north-east provinces both worms are found but the former certainly predominates

Ancylostoma braziliense, a common infection of dogs and cats and wild felines in many parts of the world, is rare as a human intestinal infection, but has been reported as occurring sporadically in the southern States of America, Brazil, West and East Africa, India and Ceylon, the Philippines, Fiji, and other South Pacific islands In some places, on the bathing beaches of Florida and São Paulo, its nuisance importance in causing 'creeping eruption' is considerable

ÆTIOLOGY

The causal organisms.—The two most important hookworms that parasitize man and reach the intestine are *Ancylostoma duodenale* and *Necator americanus,* the third, *Ancylostoma braziliense,* is rarer and less important as an intestinal parasite of man, but is more likely to give rise to a skin lesion known as 'creeping eruption' when it fails to penetrate the deeper layers of the skin

The three worms are morphologically similar, although readily distinguishable from one another in their adult and larval stages, their life cycles are identical, and all three produce very much the same clinical pictures when they parasitize man The three stages of *Ancylostoma duodenale,* the egg, the larva, and the adult, will be described and any special differences exhibited by either of the other species will be noted

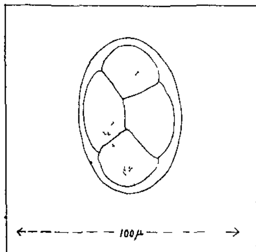


Figure 149 The egg of *Ancylostoma duodenale*

The **eggs** are colourless thin-shelled oval bodies with bluntly rounded ends, measuring on the average 40 by 60 microns Most characteristically the protoplasm

segmented stage, or with fully-developed first-stage larvae coiled within the shell The eggs of *Necator americanus* are longer (64 to 76 microns) and narrower (36 to 40 microns ... otherwise similar, and the eggs ... able from those of *Ancylostom*

The **larvae** rarely emerge from the shell within the intestinal canal, so that when a larva is found in the stools the first assumption is that it is not a hookworm larva but one of *Strongyloides stercoralis*, however, the rhabditoid larvae of this latter species have a very short buccal cavity

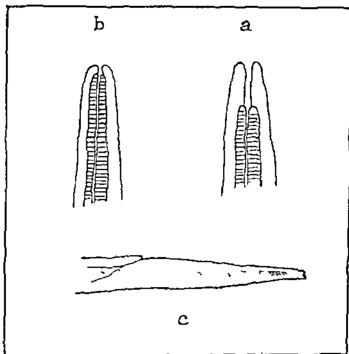


Figure 150 Showing difference between rhabditoid larvæ of *Ancylostoma* (a), and of *Strongyloides* (b), and also notched tail of the filariform larva of *Strongyloides* (c) *

(figure 150, *b*) which makes t ... itoid hookworm larvae (figure 150, *c* ... *ndes* is unmistakable on account of ...

The first stage rhabditoid larva, which is 250 to 300 microns long and 17 microns in diameter, usually emerges from the ovum within 24, or at longest 48 hours after the stool has been passed onto a suitable medium; here the larva feeds on organic matter for about another three days, sheds its cuticle, and becomes a second-stage larva which is about double the size of the first-stage This larva continues to feed and grow for another three to five days and then, when it has reached about a millimetre in length, its mouth closes up and it becomes a fully-developed third-stage non feeding filariform larva This larva sometimes retains its cuticle for a time, but sheds it before it enters its new host When it reaches the

ejunum the larva sheds its filariform cuticle attaches itself to the intestinal mucosa feeds and grows into an adult

The **adult** worms are pinkish or creamy gray in colour cylindrical, lightly curved, 8 to 13 mm in length with a greatest diameter of 0 4 to 6 mm, the **males** are distinctly smaller than the females being seldom above 11 mm in length or 0 5 in diameter whereas the **females** are seldom less than 0 6 in diameter The worms of the other two species are slightly smaller, *Necator americanus* varies from 7 to 9 mm by 0 3 for the male and 9 to 11 by 0 4 for the female and *Ancylostoma braziliense* is very slightly

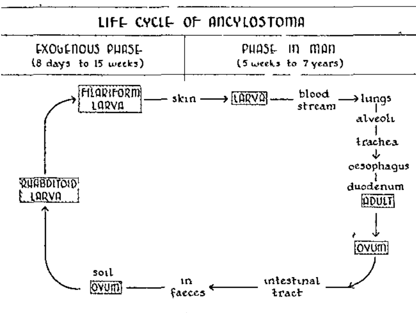


Figure 151

smaller than this but there is too much overlapping to allow the making of a diagnosis on size of the single individual alone except of course where large ones—that are necessarily *Ancylostoma duodenale*—are encountered

Hookworms are distinguished from other intestinal worms of about the same size by their dorsally flexed anterior ends and oval shaped heavily reinforced chitinoid buccal capsules In *A duodenale* there are two pairs of teeth and in *Necator americanus* a single pair of cutting plates

The life cycle of the worm—The eggs are passed in a stool by an infected individual *on to the moist soil the stool is mixed with the surface* layer of the soil by the action of rain by insects such as the coprophagic beetles or by animals within 48 hours the larvae have emerged from the eggs, the larvae migrate laterally for only short distances measured in inches but in sandy soil may burrow for a foot or more below the surface of the ground Here they develop and when they have reached the third larval stage are infective to man Returning to the surface and lying on the soil or on blades of grass or other plants, they attach themselves to the feet of passers by, and immediately burrow into the skin usually at

the side of the foot, on the dorsum or between the toes, where the skin is thin and soft They will penetrate at any other site where the skin is sufficiently thin Laboratory workers, from Looss onwards, have frequently been infected through the hands as also have miners, and bathers in contaminated waters are liable to be infected at any point on their skin surface

The larvae can penetrate the apparently normal skin, either through the hair follicles or through microscopic faults in the epidermis, they reach the blood vessels in the dermis, and, entering a venule, they are carried in the blood stream via the right side of the heart to the lungs In the lungs they penetrate the wall of an alveolus and migrate, via the bronchioles and the trachea, to the epiglottis, in this migration, they are aided by the ciliary epithelium of the respiratory tract At the point of entrance into the air sac they cause a certain amount of local damage to the alveolar mucous membrane, including localized haemorrhages At the epiglottis they pass into the oesophagus and now reversing their direction they pass into the stomach and eventually reach the jejunum, where they attach themselves to the mucous membrane and develop into male and female adult worms Not all the larvae that start from the skin reach the jejunum, some evidently die in the tissues

The adult worm is an avaricious and wanton blood sucker, that is, it takes far more blood than it needs for its own nutrition, literally pumping the blood out, at the rate of 0 67 c cm a day, it has been estimated in the case of *Ancylostoma duodenale* *Necator americanus* takes less blood 0 2 to 0 5 c cm a day

The female worm lays her eggs in the lumen of the intestinal tract, these have been variously estimated as averaging from 10 000 to 30 000 a day The egg output of *Necator americanus* is much less and is usually estimated at less than 10 000 a day

From the time the larvae enter the body to the appearance of the first eggs in the stools there is an interval of about five weeks It has been estimated that 70 per cent of adults disappear from the intestine within a year nearly all within three years, but rare instances of persistence up to 9 years have been reported Thus, although oviposition is believed not to be a continuous process, it is fairly certain that a single female hookworm will produce several million eggs during her life-time These are passed out with the faeces and the cycle begins again

The viability of the ova and larvae —If the eggs do not find their way
[illegible] will be slowed down or stopped
a long time but development is
[illegible] climate
[illegible]re
[illegible]re

fails to [illegible]

Immunity —The question of immunity in helminthic infections is not [illegible] placed on an entirely satisfactory basis but there is considerable evi- [illegible] in animals that

[illegible]
susceptible

In dogs, the development and maintenance of immunity is dependent to a large extent on their nutrition, and when ill-nourished dogs are given an adequate diet, not only do they improve in health, but they lose their hookworms and resist further infection (Otto and Kerr, 1939)

In man the

proper nutrition of the human host

The effect of diet on the development of hookworm *disease* is of course a well-established fact, but this is not necessarily an immunity phenomenon

susceptible to in-
This is possibly
the skin of children

EPIDEMIOLOGY AND FACTORS IN HOOKWORM INFECTION

The essentials for the development of hookworm *infection* in a population are

(a) The presence of one or more infected persons, as man is the only reservoir at least as far as *Ancylostoma duodenale* and *Necator americanus* are concerned

(b) A suitable terrain around a population unit—a homestead a coolie 'line' or a village, a light soil preferably a sandy loam with decaying vegetation and shade or some other special local condition e.g in a mine or tunnel

(c) Promiscuous defæcation or at least a defective sanitary system

(d) A warm humid climate (or micro-climate)

(e) A population that is largely barefooted in the hot months of the year at least and is susceptible to infection

For the development of hookworm *disease*, one should add —

(f) A sub-optimal diet for the population defective especially in iron and protein

The subject may be discussed further under each of the above six headings

(a) As has been indicated above, a single pair of worms will, during a year, give rise to several million eggs which in suitable medium will develop into a similar number of hookworms, these could theoretically cause a heavy infection in a large number of persons In nature, however, the wastage is enormous so that to maintain a high infection rate amongst the population a rich source of infection is necessary Other factors being equal, the infection amongst the population will vary with the degree of infection of the soil, which in turn will depend on the number of infected persons polluting the soil and the average number of ova in their stools

(b) and (c) Four examples under which these two conditions are optimal for the development of hookworm endemicity are given

(ii) *The village in India e g., in Bengal Behar, or Assam*—These villages are sometimes islands of slightly raised ground surrounded entirely by rice fields

illager defæcates
jot sun plays on
or larvæ and at
buried by dung
has been shown
at least taken

further afield and there is less chance of their again coming in contact with the feet of the villagers However when these fields are flooded, as in many places they are for several months each year, the defæcating ground becomes confined to a much smaller area closer to the house, and usually more shady Such conditions favour the larvæ which remain in the locality and may a few days later re-enter the same individual's feet or infect another member of the community

In other circumstances the advent of the rains will tend to wash out the larvæ from the soil and most infections will occur in the drier season

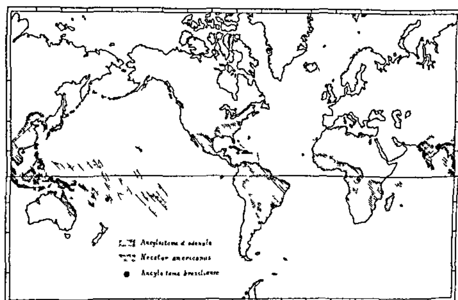


Figure 151 A

(iii) *Tea estates in India*—The tea-garden coolie is often a very primitive

Examples such as these could be multiplied indefinitely

(*d*) Hookworm infection is confined to hot countries, except where in cooler countries the local conditions, *e g*, *in a mine or tunnel*, simulate those of a hot country In subtropical countries, during the months when the night temperature falls below 50° F, larvae will seldom be found in the soil and no infections will take place during these months, *e g*, in Alabama from December through March Similarly, in hot dry countries the larvae die when the saturation deficiency rises above a certain figure, but this figure depends to some extent on the nature of the soil, in India,

Chandler (1927) found that 6 inches of rain per month was usually necessary to insure transmission of infection

In humid areas on the other hand Maplestone (1932) found evidence that the largest number of new infections were acquired in the warm months prior to the onset of the rainy season When the rains started the ground became water logged and unsuitable for larval development

In mines infection seldom occurs if the temperature is below 70° F and conditions only become optimal in the region of 78° F

(e) Shoes or boots even if they are not defective are not a complete protection against hookworm infection European planters in India or Indian overseers who have to walk through the highly infective mud in tea gardens although they may wear good leather boots frequently become infected but of course the infection rate is much lower than amongst the barefooted Indian labourer The children in particular of the poor whites in the southern part of the United States usually go about barefooted at least in the summer time and in India and other eastern countries the majority of the labouring classes are always barefooted

Miners in European mines at least usually wear boots or shoes but in these the infection occurs through the hands from the soil contaminated rungs of the ladders

There is no evidence that there is such a thing in man as complete immunity to hookworm infection Negroes are not so readily infected as white persons in the southern states of America but in India little difference in racial susceptibility has been noted Children appear to be more susceptible than adults There is evidence that immunity is to some extent dependent on nutrition (*see* Immunity p 612)

(f) Whilst immunity to infection is uncertain there is no possible question about the effect of diet on the morbidity produced by the infection The heavier the hookworm load in comparable population groups the higher will the morbidity rate usually be but this direct correlation between the hookworm load and the degree of anæmia for example in the individuals of a group is often absent This is probably a matter of individual differences in diet and iron assimilation There is evidence that if the intake of iron is sufficient there will be no anæmia however heavy the hookworm load and further the writer has frequently been able to show that even in the presence of a very heavy hookworm infection it is possible to bring the hæmoglobin level back to normal by iron administration alone Similarly we (Napier and Das Gupta 1937) have shown that a high protein diet will produce a general improvement in the condition of patients suffering from hookworm disease causing the disappearance of the œdema

Special circumstances and other factors—Whilst the above discussion probably covers 99 9 per cent of hookworm infections there are exceptional circumstances under which infection may be acquired vicariously *e g* in the laboratory and by bathing in water heavily contaminated by fresh sewage (Ashford *et al* 1933) Dogs pigs and jackals commonly eat human faeces Sor
but many survive so
fection Cockroaches
destroys the ova and
should therefore be encouraged

PATHOLOGY AND SYMPTOMATOLOGY

Variations in the clinical picture—The morbidity will depend on four circumstances—(a) the species of the worm, (b) the duration of the exposure to infection, that is, whether it was a single incident (acute) or a repeated one (chronic), (c) the weight of the infection, and (d) the tolerance of the host

(a) **Species**—*Ancylostoma braziliense,* the dog hookworm, frequently fails to reach the blood stream and so may produce only dermal lesions Although there are some localities where this species is capable of producing the full syndrome, it is undoubtedly the least pathogenic of the three species Between the pathogenic potentialities of the other two species, there is less difference, but *Ancylostoma duodenale* is the more pathogenic So that the ascending order of pathogenicity is *Ancylostoma braziliense, Necator americanus* and *Ancylostoma duodenale* Mixed infections are common

(b) **Duration of exposure**—The infection is usually a more-or-less continuous or at least an oft-repeated process, but rare instances have been reported in which single heavy infections have occurred (Ashford *et al* 1933) these latter have given us a valuable glimpse of the pathological processes that probably occur in all cases but which, being as a rule spread out over so long a period, have been difficult to appreciate clinically

(c) **Weight of infection and** (d) **host tolerance**—The clinical picture shows considerable variation with the weight of the worm infection and the tolerance of the host In most areas the majority of infections are symptomless throughout, while, in others, clinically apparent infections predominate The severity of the symptoms will, on the whole, vary in the direct ratio to the weight of the infection, but there will be many individual exceptions, due to variations in host tolerance (*vide supra*)

Skin lesions—At their point of entry, the filariform larvae cause a local irritation, no doubt partly on account of the organisms that they carry with them from their septic environment As indicated above, this is usually at the sides of the foot, or on the dorsum between the toes, where the skin is soft and thin Within about half an hour of the entry of the larva there is a burning sensation and later the area becomes intensely irrita[illegible] n the
cour[illegible]
and[illegible]
septic organisms, so that the [illegible]
contents or become pustular These vesicles or pustules, which are usually multiple coalesce and finally an eczematous patch develops This condition is known as '**ground itch**' or '**water sores**', *for obvious reasons*

There is some evidence that this local condition is more frequently caused by *Necator americanus* than by *Ancylostoma duodenale,* for it appears to be rare in Egypt where the latter only is found whereas in India where both worms are found, it is relatively common, especially amongst *tea-estate labourers*

The pathology of '**creeping eruption**' is somewhat different, as it is dependent on the fact that the larvae of *Ancylostoma braziliense* the dog hookworm is often unable to penetrate all the layers of the skin, after penetrating the epidermis, the larvae wander laterally between the epidermis and the corium in an aimless manner for a considerable time, causing a local reaction There is local infiltration by eosinophils and

neutrophils with local hyperæmia and œdema and later vesicl
. sicles along its old tracks
atched off and the area
The tracks of the larva
regularly twisted threads
move at the rate of several centimetres in twenty four hours a
duce extensive patterns throughout the skin surface of a l
survive in this intradermal locus for several weeks or even

Occasionally, the larvae of the other species cause a simila

The larval phase.—In synchronized heavy infections (acu
evidence that some larvae do not immediately find their w
venules of the skin, but wander in the deeper tissues taking a
to reach the lung or perhaps never reaching it at all being p
in the tissues In such cases acute general symptoms *e g* f
may simulate typhoid, and a sharp eosinophilic (75 per cent) l
have occurred It is doubtful if in the ordinary spaced infect
ever any trace of this syndrome beyond a moderate increase in

The lung lesions.—The next point at which the worm mak
ence felt is in the lungs In escaping from the lung capillar
air sacs it penetrates the alveolar mucosa often causing subr
travasations of blood which may even reach the cavity of the
lead to collections of blood that are later coughed up by t
Pneumonitis has been reported but is rarer than in the cases
and strongyloides infections In cases in which there is an ac
a heavy synchronized infection there may be a sensation of
in the throat [illegible]

Ga[illegible]
nounc
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comfort is a common symptom it often persists and may b
evidence of the infection In heavier infections that have b
over a long period especially in poorer class Indians and other
populations these gastro intestinal symptoms stand out from t
the picture of ill health The diarrhœa may be due to the local
and the absorption of metabolites in the intestine, but Ashfor
coworkers (1935) believe that it may be the result of helminth
olites from the live or dead larvae that have gone astray in t
(*vide supra*)

In the acute case, if there is no further infection, the acute
will tend to subside as the adult worms settle in the jejunum, l
infection has been a [illegible] one and the worms are not remove

General symptoms in established (chronic) ancylostomiasis—When the adult worms are established in the jejunum they suck blood, possibly inject some 'toxin', and make small lesions in the mucosa which may allow septic absorption The recognized syndrome of ancylostomiasis will now develop

The fully-developed ancylostomiasis syndrome shows a patient with œdema of the extremities and face—the puffy pale ancylostomiasis facies —mucous membranes almost white, hair scanty, and a protuberant abdomen The patient has a vacant expression he has no energy and is indifferent to his surroundings He complains of palpitations and is breathless on exertion He suffers from dimness of vision and night-blindness Examination shows that his heart (both right and left side) is extremely dilated there is usually a mitral systolic murmur and sometimes one at the pulmonary base, his pulse is rapid, and his blood pressure low His tongue has a wash-leather appearance and often a black streak down the centre A watery diarrhœa is common

The cardiac changes, which are all secondary, to severe endocardial damage that is in turn caused mainly by the anæmia are easily reversible when the blood picture is improved by anti anæmic treatment alone, but there are a few cases in which this improvement will be delayed until the worms are expelled, this suggests a possible second factor of a toxic or an allergic nature (Heilig, 1942)

Patients will usually have taken several years to reach this miserable state and in the case of children their physical and mental development will have been retarded, so that a child of 16 years of age may physically and mentally appear to be no older than 10 years, and at the same time he will lack the childish energy and desire to play with other children *Sexual maturation is also retarded A curious craving manifested by* geophagy (or eating of earth), often develops

The anæmia is perhaps the most striking morbid change and it is certainly the most easily measured so that the blood picture will be discussed in some detail

Blood picture—***The cause of the anæmia***—Until a few years ago there was much difference in opinion on the actual cause of hookworm anæmia It is now well established that it is a true secondary anæmia due ... mping large quantities of blood from the ... f the intestinal canal The lost blood ... be done at the expense of the reserves ... rming substances Even with a heavy load of worms anæmia can be prevented or even cured by giving the patient a good protein diet plus medicinal iron but in persons living on the borderline of iron starvation anæmia will be caused by quite a moderate load

While most cases can be cured by iron administration alone (*vide infra*) there are a few exceptions in which the normal blood level cannot be regained without the removal of t ... that the worms may also introduce some toxin or al ... tion However in a small series of ... examinations and sternal puncture ... and Majumdar, 1941) failed to see any evidence of the repressive effect on the bone marrow of the hypothetical toxin and we suggested that these few exceptions might be the result of malabsorption of some essential blood-

forming element as a result of course, of dysfunction cau ed by the hookworm infection

The nature of the anæmia —A more striking reduction in hæmoglobin can occur in hookworm disease than in any other disease of equal serious ness The writer has seen tea estate coolies walking into the dispensary with a hæmoglobin percentage that was estimated by the tea estate doctor as 5 per cent on the Tallqvist scale The blood that came out when one pricked the finger of such patients was a thin watery fluid which would not make a proper smear even on a scrupulously clean slide The colour was in fact, well below the 10 per cent matching on the Tallqvist scale and by more accurate methods a figure of 1 5 grammes of hæmoglobin per 100 c cm of blood was not an unusual finding with 900 000 red cells per c mm and a packed cell volume of 6 per cent this gives a mean corpuscular hæmoglobin

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not usually

There are usually a few normoblasts present and 2 to 5 per cent of reticulocytes the van den Bergh reaction is negative

There is often an increase in blood volume this compensates to some extent for the extreme anæmia and possibly explains why patients can live and even work with such low percentages of hæmoglobin There is a de crease in the serum proteins and in both calcium and cholesterol

The white cell count —The total count is usually between 5 000 and 10 000 per c mm That is more or less normal but the eosinophil percent age is usually raised An average count of 14 per cent is not unusual but in the very heavy infections the count is often within normal limits or eosinophils may even be absent

Gastric acidity —There are conflicting statements in the literature on this subject We found in a series of 28 Indians that the gastric acidity was normal or increased in 21 (or 75 per cent) and that the relation be

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sibly an independent contributory factor in the cause of anæmia There were in this series only three cases of complete achlorhydria Anti anæmic treatment causes no striking improvement in the acidity

Fæces —The stools are watery As well as the ova which will be dis cussed below, there is nearly always occult blood

DIAGNOSIS

In the parenteral phases —The diagnosis of the '**ground itch**' would be difficult without the epidemiological background and the condition is likely to be confused with the secondary pyogenic invasions in tinea infec tions and of other skin conditions but '**creeping eruption**' produces a map like effect on the skin that is very characteristic *Gnathostoma sp ni*

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to ca

only

or the fly-maggot from the lesions There is little opportunity to make an accurate diagnosis at any other stage of the parenteral infection, although in a few cases larvæ have been coughed up from the lung

In the intestinal phase—The clinical picture of hookworm disease is a characteristic one and so also is the anæmia (*vide supra*), but it would not be justifiable to make a diagnosis without the confirmation of stool examination The finding of hookworm ova in the stools is evidence of *hookworm infection*, but, even when the ova occur in relatively large numbers and the patient is anæmic, this is not necessarily evidence of *hookworm disease*, as the anæmia may have some other cause Many populations have an infection rate of almost a hundred per cent without much morbidity directly due to the worms, and great care must be taken to view these hookworm infections in their proper perspective and not attribute either too much or too little to them In the early days several experienced investigators made serious mistakes in this direction (*e g* Giles in Assam attributed kala-azar to hookworm infection) In the absence of other obvious causes of illness, and on the finding of perhaps a single egg, it is often tempting to label a patient 'ancylostomiasis', but this should not

very thorough investigation to exclude
therapeutic test On the other hand,
ial groups, in Europeans in India for
ild but troublesome gastric-intestinal
igastric discomfort, and they should

not be ignored

Examination for ova—It will be possible to make a diagnosis in any clinically significant infection, and even a rough estimate of the hookworm load by a direct examination of a stool emulsion under the microscope, but for recognizing very light (initial or residual) infections for example in testing the efficacy of a drug, concentration (*e g* floatation) methods should be used

Technique

on a large micro-
a thin emulsion is

placed

In the absence of a centrifuge the zinc sulphate solution can be added directly to the fæces mixed thoroughly and allowed to stand for a few minutes after which the floating ova are collected on a coverglass in the way described above

Lane's direct centrifugal floatation method which entails the employment of a special apparatus is dependent on the same principle it is possibly the best method

for finding the last egg in a stool but the former of the methods described above falls very little short of Lane's method and is sufficiently accurate for all practical purposes

Estimating the hookworm load—The methods for doing this *before* treatment are necessarily rough, but it is generally considered that one female worm will pass enough eggs to represent 80 eggs per gramme of stool, and on the assumption that the sexes are equally divided, this means that each 40 eggs per gramme represents one worm

We have adopted the principle of grouping hookworm loads as follows —

I	Light load	= under 2000 eggs per gramme
II	Moderate load	= over 2000 but under 10 000 eggs per gramme
III	Heavy load	= over 10 000 but under 40 000 eggs per gramme
IV	Very heavy load	= over 40 000 eggs per gramme

The last figure is equivalent to a load of 1,000 worms

After treatment the worms can be counted by collecting all the stools for 48 hours and washing them through a fine (1-mm mesh) copper sieve The adult worms will be held back by the sieve and can be counted

There are several methods for estimating the number of ova but the following modification of the original Stoll method is in the writer's experience the best —

Technique—A test tube of suitable size is marked at the 27 c cm and the 30 c cm levels Decinormal sodium hydroxide is poured into the tube up to the 27 c cm level and portions of stool added until the fluid reaches the 30 c cm level The

cover-
l This

Other diagnostic aids—Instances have been reported in which, though no ova were found in the stools, adult worms were found post mortem The usual explanation is that these have all been male worms If this state of affairs is suspected, the therapeutic test and careful examination of the stools for adult worms should clear up the point

The finding of an eosinophilia will naturally lead to a suspicion of some helminth infection, but will be of no real diagnostic value, further, when the infection is a heavy one and the morbidity considerable, there will usually be no eosinophilia

TF at.

delayed for any reason the ova may
will have to be differentiated from
he most striking point of difference
latter In extreme cases filariform larvæ may develop, but the differentiation of these from the filariform larvæ of *Strongyloides* presents little difficulty as the latter have a notched tail that is quite characteristic

PREVENTION

Introduction—It will first be necessary to make an accurate assessment of the problem to be faced This will require a clinical survey of representative groups of the population, including at least some rough estima-

tion of hæmoglobin an examination of the stools preferably of the same

passing (*see* p 621) than by working out an average for the whole number examined—and finally, if possible an estimation of the infectivity of the soil* in areas where most infections are thought to occur, this last investigation should be made at several different times of the year These examinations will have to be repeated periodically to measure the success or failure of the procedure (For short descriptions of the methods of stool examination *see* p 620)

In order to obtain a view of the subject of prevention in proper perspective it should be considered under two headings namely, (I) the prevention of hookworm infection and (II) the prevention of hookworm disease, despite the fact that there will be much overlapping in the two aims

(I) **Prevention of infection**—The reader is asked to turn back to p 613 where the five essentials for hookworm infection are given we will consider the subject under each of these five headings

(*a*) Man is the sole reservoir of infection of the two important species so that effective anthelminthic treatment will have the double result of curing the individual and reducing the source of infection in the community

(*b*) The circumstances are such that it is seldom that anything can be done to improve the terrain, but where the area is a very limited one as in mines attempts have been made to reduce its suitability as a medium of infection by treatment with such substances as common salt

(*c*) The proper disposal of human fæces by installation of sanitary latrines and the encouragement—or the enforcement—of their use by the whole population is the crux of the whole hookworm problem, and where this is possible all other preventive measures become subsidiary This is
ill naturally vary with the condi
red hole latrine has been a very
of this system obviates the preju
communal latrine It is of the
utmost importance that any scheme that is introduced should be easily workable and suited to the special circumstances it must not be liable to break down as an unsatisfactory latrine will do more harm than good This aspect of prevention is so important that it must always be remem

* *Estimation of larvæ in soil*—This is most easily accomplished by the Baermann technique which depends on the fact that larvæ will migrate out of soil into warm water that comes in contact with the lower surface of this soil The technique is described by Craig and Faust (1943) as follows —

The simple apparatus used consists of a glass filter funnel of 15 to 23 cm

sediment poured on to a slide for examination The examiner needs con [illegible] skill and experience to differentiate hookworm and *Strongyloides* larvæ from nematodes free living in the soil

bered that, whatever other measures are taken, the only enduring solution will be proper disposal of human excreta, the source of infection, and a beginning must be made to this end

Education and propaganda will play an important part in the prevention scheme, as not only has understanding to be imparted, interest aroused and ingrained habit broken, but quite often active prejudice has to be overcome

Where human excreta is used for manure, either septic tank treatment for a considerable time, at least 3 months in a temperate climate, or six weeks in a tropical one, or some other means of 'sterilization' must be employed, *e g* the addition of lime to a dilution of 1 in 500 or mixture with litter to make a form of compost and burial in the earth which will raise the temperature sufficiently to destroy the eggs and larvæ But this particular problem is a difficult one and has not yet been satisfactorily solved

(*d*) Climatic conditions are matters outside human control

(*e*) The wearing of good boots or shoes will decrease the chance of infection but not stop it completely Unless this is an entirely foreign custom amongst the people, the wearing of boots or shoes should be urged Propaganda will again find an important place here

II **Prevention of hookworm disease.**—It is again necessary to recapitulate Certain facts must be remembered

(i) Hookworms do not undergo any multiplication within the body of the host so that without re infection there will be no increase in their number but in fact a relatively rapid reduction (placed at 70 per cent in the first year by some observers) will occur If the infection is not to die out it will have to be repeatedly replenished We thus have the equation

$$\text{hookworm load} = \frac{\text{the rate of acquisition of infection}}{\text{the rate of worm loss}}$$

(ii) The hookworm load at any particular moment will vary from one worm to several thousand and similarly the infection may be either sub clinical or symptomatic however the relation between these two facts is not a simple and direct one but morbidity is dependent also on the tolerance of the host or in other words

$$\text{morbidity} = \frac{\text{hookworm load}}{\text{host tolerance}}$$

(iii) Host tolerance is dependent on certain fixed factors such as age and race, but it is also influenced considerably by a variable factor the diet of the host

The eventual aim of prevention is the reduction of hookworm morbidity in the population It will be seen from the above equations that this can be done by

(*a*) reducing the hookworm load or
(*b*) increasing the tolerance of the hosts

The hookworm load can be reduced by

(*c*) decreasing *the rate of acquisition of infection* or
(*d*) increasing the rate of worm loss

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The only practicable measure for achieving (*b*) increase in tolerance, is also by dietary improvement

* Referring to the number of worms that actually reach the bowel

Thus to summarize hookworm morbidity can be reduced by —

(i) Improvement in environmental hygiene (*sensu lato*)
(ii) Anthelminthic treatment
(iii) Improvement in diet

It must be quite obvious that if the rate of the acquisition of infection is sufficiently decreased by sanitary improvement or the rate of worm loss is sufficiently increased by mass treatment or both effects are brought
line and the average
the morbidity level
ed this end will be
achieved at an earlier date In this way the morbidity in the population may be reduced without achieving the ideal of a perfect sanitary system which in most cases will be impossible or the complete deworming of the community which in most cases will be impracticable The great disadvantage of this method of approach is that continued vigilance to ensure that there is no dangerous increase in the hookworm infection in the population and usually periodic retreatment will be necessary

Policy —There have i
realistic school demanded
lines indicated in the last
tion of this morbidity in
that the aim should be the
this being measured in terms of the number of infected persons left in the population

We will consider the latter first It is impossible to criticize the ideal but how far is the aim practicable? To achieve complete success not only the symptomatic cases but every member of the population who shows any hookworm infection must be treated (if he will consent) To ensure the removal of all the worms even by the most efficient method at least three treatments will be required in a large number of cases and an elaborate method of stool examination will be necessary to check the results Further this whole process will usually have to be repeated at monthly intervals for a period of four months to catch all the fresh worms—those migrating in the tissues and those acquired from larvæ surviving in the soil since the first mass treatment—before they can produce any eggs Even then a few worms may escape and should complete success be achieved a casual

success would be so improbable that it would be scarcely worth attempting

The policy of the realistic school is the one now generally adopted Complete treatment of the whole community is not usually attempted but treatment is concentrated on the members of the families or of the habitation groups in which any cases of hookworm disease are found one course of anthelminthic treatment is given to each member and medical treatment for the anæmia *plus* a second course of anthelminthics if necessary to those with clinical evidence of the disease The most favourable time for giving such a course of treatment is during the period—when there is one—in which transmission does not occur *e g* in the southern states of America the temperature prevents transmission between November and March

By this modification of the mass treatment programme much time-consuming laboratory work is saved and the number of treatments given is

reduced very considerably although it may be advisable to repeat the treatment every few years It has been found that if this procedure is combined with the provision of latrines and the dissemination of propaganda regarding their proper use a steady decline in morbidity will take place year by year

In conclusion, it must be remembered that none of these measures mentioned above can be put into effective operation without explaining to the people the cause of the disease and the necessity for their whole hearted cooperation so that to the measures summarized on p 624 must be added

(iv) Education and propaganda

TREATMENT

This must be considered under the two major headings (I) treatment of the parenteral infection and (II) treatment of the intestinal infection and the latter can be divided into (a) specific treatment and (b) general treatment

I **The parenteral infection** —Except that in the case of creeping

II **Intestinal infection** —(*a*) **Specific**

Historical —Prior to about 1917 chloroform beta naphthol and thymol were the principal drugs used of these thymol was undoubtedly the best A dose of

drugs have since been introduced it only deserves mention in an historical section

Chloroform and oil of eucalyptus was the standard treatment for this and other helminth infections in the early days of the century and deserves honourable mention whereas beta naphthol is quite useless in safe doses and it is difficult to see why it was ever advocated

chloride or tetrachlorethylene but given alone for hookworm infection its effective dose (3 c cm for adults) is dangerously near its toxic dose so that it has been superseded except for mixed infections

In 1922 Leach used carbon tetrachloride in man a drug that had been used successfully in dogs by Hall and it was later used in hundreds of thousands of

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adult
same w
on the

In 1935 ...

... used It appeared too late to be used in ... atment campaigns so that it was slow in ... s However, it has now been used in ... very few ill effects and no fatalities have been reported A single treatment may be expected to remove 99 per cent of *Necator americanus* and 96 per cent of *Ancylostoma duodenale*

Tetrachlorethylene (C_2Cl_4) is undoubtedly the drug of choice It is best given in the form of a suspension in saturated sodium sulphate, 4 c cm of tetrachlorethylene is shaken vigourously in a stoppered bottle containing two ounces of saturated solution of sodium sulphate and then taken by the patient before it has time to settle

The dose for children is 0 2 c cm for each year of age The drug should be taken early in the day on an empty stomach Some workers advocate ... water the night ... difficulties about ...

The only ill-effects are a slight sensation of giddiness and in some cases exhilaration as occurs after taking alcohol The treatment may be repeated in a week's time if necessary

If there is a mixed ascaris and hookworm infection, oil of chenopodium, 1 c cm, should be added to the tetrachlorethylene under the same routine

Hexylresorcinol (1 3-dihydroxy-4 hexylbenzol), although slightly less efficacious than tetrachlorethylene, has a special use in seriously debilitated patients It is the least toxic of the anthelminthics in general use, it is given in one gramme doses, in five hard gelatin capsules containing 0 2 gramme each The dose for children under 6 years is three capsules (0 6 g) and for older children 4 capsules, (0 8 g) The capsules, which must be swallowed and not bitten or a local-irritation will be caused, are taken on ...

Checking results of treatment —If this is to be done accurately the stools must be screened for dead worms (*vide supra*), but for mass treatment it will seldom be possible to do anything more than examine the stools for ova This should be postponed until about the seventh day after treatment, as otherwise eggs passed by worms before the treatment was given may be encountered and vitiate conclusions If there are still more than 200 eggs per gramme, the treatment should be repeated

(*b*) **General** —Malnutrition is a common accompaniment of hookworm infection and whenever possible a general dietary improvement should be instituted An increase in the intake of both iron and protein is particularly indicated, however, the improvement in the anæmia need not be unnecessarily delayed by relying on dietary iron but medicinal iron should be given whenever necessary It has repeatedly been shown that ... will effect little if any ... 152), but on the other ... it is possible to bring the blood level up to normal by iron administration alone and to very ... on prior to the ad- ... a second course of ...

Iron can be given conveniently in the form of ferrous sulphate tablets, grs vi, three times a day for 21 days a total dose of 378 grains, or better

still in a mixture For the mixture, 12 grains of ferrous ammonium sulphate ($Fe\ SO_4\ (NH_4)_2\ SO_4\ 6H_2O$), in half an ounce of dextrose, is taken three times a day for 21 days The *iron* content of the mixture is a little less than that of the tablets, even though the dose of the salt is doubled but none the less the response to the mixture is usually more rapid Two

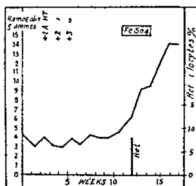


Figure 152 Showing absence of effect on hæmoglobin level of three doses of 3 c cm of C_2Cl_4 + 1 c cm oil of chenopodium within a period of 8 weeks and immediate effect 18 grains of ferrous sulphate daily

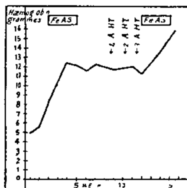


Figure 153 Showing the immediate effect of 18 grains of ferrous ammonium sulphate daily before deworming

21-day courses of iron are usually sufficient to bring the hæmoglobin to normal even in the most severely anæmic cases the result of treatment should be checked by blood examination

The writer questions whether it is ever necessary or even advantageous to give a blood transfusion in an ordinary case of hookworm infection however severe the anæmia, in view of the extremely rapid response to iron that can be expected, but in the special case, *e g* of the pregnant woman who is nearing full-term, this will perhaps be indicated

PROGNOSIS

From the public health point of view the chances of ridding a population of hookworm infection will depend on how much sanitation it will be possible to install, if money is the limiting factor or on how much the population can be induced to take advantage of the sanitary conveniences installed, if ignorance and custom, religious or otherwise, are the main handicaps against which one has to work In most countries where a de-

rove sanitation the hookworm posi-

in five or six years where this has

signs, very appreciable improvement

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medicinal iron are given, even the most anæmic patient may be restored to good health within as short a time as a month

Unless the patient is first seen *in extremis* death should never occur in an *uncomplicated case of ancylostomiasis*, but in the very anæmic patient treatment for the anæmia should be given first

The pregnant woman, however, with severe ancylostomiasis often fails to survive parturition On the other hand, if the anæmia is solely due to the ancylostome infection and is therefore an iron deficiency anæmia, the chances of survival of that inexorable parasite, the fœtus, who appropriates all the iron it requires, are good (Napier and Edwards, 1941)

STRONGYLOIDIASIS

Introduction.—It may be said of this infection that clinicians tend to pay it too little and helminthologists too much attention in proportion to the pathogenic proclivities of the parasite and the extent of its incidence The explanation for the attitude of the latter is not difficult; this worm has a complicated and variable life cycle, unique in helminthic infections, that includes an extensive sojourn in the human tissues that might reasonably be expected to call forth considerable tissue reaction On the other hand, there is little doubt that while serious infections are common enough to make the dismissal 'pathogenicity doubtful' of some textbooks quite unjustifiable, the total amount of morbidity and mortality that this worm produces, directly or indirectly, throughout the world, is infinitesimal compared with that caused by the hookworm

Geographical distribution—This is world-wide, but mainly tropical, and the *infection is particularly associated with the more humid tropical* areas It is obviously far more common in the southern states of North America and in South America than in the tropical areas of the eastern hemisphere (Faust, 1936) It is relatively uncommon in China and in India, although in *the latter the writer has seen a number of instances of* this infection in which there was some degree of associated morbidity

EPIDEMIOLOGY

The conditions which favour this infection are roughly those which favour [illegible] certain differences in the [illegible] allelism in the intensity [illegible] erent parts of the endemic areas

There is a distinct male predominence amongst the persons infected, and the age groups with the heaviest infection rates are in the second decade

The incidence is often high in institutions, such as mental hospitals

ÆTIOLOGY

The causal organism.—The stages through which the worm passes are as follows

The egg.—This is fully embryonated on discharge from the uterus, it is deposited in the tissues in the parasitic phase and is seldom seen except in experimental infections It has a thin transparent shell, is ovoid in shape, and measures about 54 by 32 microns

The rhabditoid larva—*This develops* from the egg in the tissues, reaches the lumen of the gut, and is passed, usually as such, in the fæces

It is about 250 microns in length and can be distinguished from the hookworm larva by its shallow buccal cavity (figure 150, *b*)

The filariform larva—This develops from the rhabditiform larva usually outside the body, but also in other instances within the intestinal canal It is a long (about 1 mm) fine larva with a long œsophagus and a distinctly notched tail (figure 150, c) Occasionally, dwarf filariform larvæ develop from the rhabditoid larvæ in the intestinal canal

free-living
the para
he **male** is
ry similar
in the free-living parasitic phases

The life cycles—The filariform larva is the infective stage The larvæ *enter the skin of man in the same way as the ancylostoma larvæ*, but

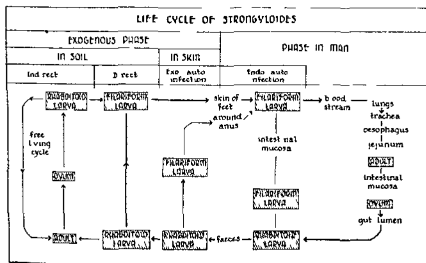


Figure 154

also through the buccal or pharyngeal mucous membrane, reach the lungs *via* the blood stream, and penetrate into the alveoli They may develop into adults here, but otherwise they ascend *via* the bronchi and trachea to [illegible]
the
wh
in
eggs a day Within the mucosa the eggs develop into rhabditoid larva which work their way out into the bowel lumen and pass out with the fæces The whole journey takes about a month These larvæ feed on organic matter in the soil

One of two things will now happen

If the larvæ find themselves in a sub-optimal medium, they develop into non-feeding filariform larvæ which are the infecting forms, they enter another host, and the **direct** parasite cycle is complete

Or, if conditions are optimal, then the rhabditoid larvæ feed, pass through one moult, feed again, and develop into free-living adults, these mate, the female lays eggs which develop *into rhabditoid larvæ in the soil*, and the free-living cycle is repeated, probably an infinite number of times as long as conditions remain favourable, but, when they cease to be so, the rhabditoid larvæ develop into filariform larvæ, which, though they will survive as such in the soil for many months, are immediately infective and capable of entering another human host to complete the **indirect** parasitic cycle

t go back to the ng on to the soil around the anus re-enter the skin larvæ may not pass out of the intestinal canal at all, but develop into filariform larvæ, usually the dwarf forms referred to above, and penetrate the bowel wall to cycle The former of these last two called by him 'auto-infection', and perinfection '*

our parasitic cycles, (a) *endo-auto-* infection (Faust's hyperinfection), (b) exo-auto-infection (Fulleborn's auto-infection), (c) direct (comparable to that of the hookworm), and (d) indirect in which the free-living cycle is interposed (*see* figure 154)

***Discussion.**—The practical significance of the auto-infection cycles is* that an individual can apparently retain the infection almost indefinitely without renewing it from outside The auto-infection cycles are nowhere common but are more important in temperate climates where both conditions for the survival and opportunities for the re-entry of the parasite climates sible for the soil, Another is *that* oral infection is apparent that an infection can be initiate le entry through the skin of the feet or hands

Contributory factors in determining morbidity.—There is considerable evidence that diet is a very important factor in determining patho- dual In disease, deeply

PATHOLOGY AND SYMPTOMATOLOGY

As in the case of hookworm infection, this worm produces pathogenic lesions commonly at three points on its course, (a) in the skin at the point of entry, (b) in the lungs, and (c) in the intestinal mucosa, and rarely in the bronchi and trachea

* *The word 'hyperinfection' seems* a most unfortunate choice for this cycle The word is well established in medical language as meaning 'a very intense infection' This cycle is certainly auto-infection, but if it is desirable to differentiate it from Fulleborn's auto-infection—and from a practical point of view it is questionable whether it is necessary—then the words 'exo-auto-infection' might be used for the Fulleborn cycle and 'endo auto-infection' for the Faust cycle

(*a*) **The skin** —Here the filariform larvæ may produce petechial hæmorrhages at their points of entry The site later becomes very irritating and there may be a localized œdema

(*b*) **The respiratory tract** —Hæmorrhages may be caused in the lung and these may be associated with a cellular exudate into the alveoli This frequently causes a cough during which blood stained sputum containing larvæ may be brought up and after heavy infections an atypical pneumonia may occur Occasionally the worms mature in the lungs and invade the columnar epithelium of the bronchi and trachea causing a local exudate The respiratory lesions and symptoms are likely to be greater in this infection than in ancylostomiasis

(*c*) **The intestinal tract** —The adult females invade the mucosa as deep as the muscularis mucosæ and cause desquamation and occasionally sloughing of the mucous membrane with abdominal discomfort or pain sometimes a frank dysentery but more usually a profuse watery diarrhœa or diarrhœa alternating with constipation loss of weight and indigestion The infection is often associated with insomnia restlessness and depression

The blood picture —There is usually a slight leucocytosis with an 8 to 10 per cent eosinophilia at first and later a leucopenia There may be some slight degree of anæmia usually of the macrocytic nutritional type

DIAGNOSIS

This can be made by finding the larvæ in the stools Concentration of the stool will facilitate this The larvæ appear in the stools intermittently and therefore no importance should be attached to a single or even several negative findings Further the larvæ may die and be digested during their relatively long journey down the intestinal canal thus in a case in which the infection is strongly suspected some workers recommend that a duodenal aspiration should be done Or the larvæ may be coughed up in the sputum

The larvæ must be differentiated from the hookworm larvæ the main point of difference is the shallow buccal cavity in the strongyloides rhabditoid larva and the notched tail in the filariform larva (*vide supra*)

PREVENTION

The main measures to be adopted are those employed against hookworm infection (*quod vide*) In addition the existence of this infection [illegible] nt in sanitation [illegible] in the prepara[illegible] ater supplies are [illegible]

Improvement in the diet of an infected population or individual will help to prevent the more serious results of infection

TREATMENT

This has been very disappointing as none of the anthelminthics that have been so successful in the treatment of ancylostomiasis have proved of any value in this infection Gentian violet is considered the only specific but this has not been successful in the hands of all workers in some cases this was possibly because they did not adopt the right technique but there is evidence of a variable resistance to treatment Experiments have shown that this drug will penetrate at least as far as the muscularis mucosæ

TAPEWORM INFECTIONS

Introduction—There are three important large intestinal tapeworms that infect man, namely

Tænia saginata Goeze, 1782, the beef tapeworm

Tænia solium Linnæus, 1758, the pig tapeworm, and

Diphyllobothrium latum (Linnæus 1758) Luhe 1910 the fish tape worm

and two dwarf tapeworms

Hymenolepis nana (v Siebold 1852) Blanchard 1891
Hymenolepis diminuta (Rudolphi 1819) Blanchard 1891

LARGE TAPEWORMS

[illegible] None of these infections is tropical in its
end for their distribution upon the
ious countries and, as the control of
countries the meat-eating sojourner
infection with either the pig or the
beef tapeworm in a tropical country than in the United States or in any of the western European countries In eastern Europe the pig tapeworm especially is relatively common

The fish tapeworm on the other hand is rare in the tropics, and occurs in the Baltic countries northern Italy and Switzerland in the Danube delta, in Palestine in Siberia Manchuria and Japan in some places in the northern states of America and in Canada and sporadically elsewhere In the last named countries the foci of infection are mostly on the shores of the great lakes where the infection was probably introduced by Scandinavian immigrants but recently a focus has been found in Florida

ÆTIOLOGY

The parasites —The tapeworms are flat hermaphroditic worms consisting of —(i) a scolex the so called head which is an attachment organ (ii) the neck which is narrow and formed by a number of undifferentiated proglottids (iii) a short section of differentiated but immature *proglottids or segments in which the male and female sex organs are present* (iv) a long section of mature proglottids and finally (v) the gravid proglottids These worms have no digestive tracts but absorb nutrition from their environment in the gastro intestinal tract of their hosts The life cycles of the different species vary so much that it will be necessary to describe them separately

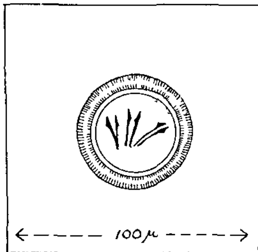


Figure 156 The egg of *Tænia saginata* that of *T solium* is identical

Life Cycles

Tænia saginata —Man is the only important definitive host he passes the proglottids in his fæces and, when these disintegrate, the ova, which are

spherical, 30 to 40 microns in diameter, have a thick shell and contain an onchosphere with *three pairs of hooks, are set free* These are ingested by cattle, in whose gut (duodenum) onchospheres emerge and penetrate the bowel mucous membrane, reach the systemic circulation and are filtered out in the muscles Here they develop into cysticerci in about 60 days These cysticerci which are white oval bodies 7 to 10 by 4 to 6 mm are the infective form for man who ingests them in raw or under-cooked meat From the cysticerci the worm develops, attaches itself to the small *intestinal mucosa*, and proceeds to grow into a mature worm, measuring from 4 to 10 metres with as many as 2 000 segments, in about three months Gravid proglottids now begin to drop off one by one, pass out of the anal orifice under their own power *or in the fæces, and the cycle is complete*

Tænia solium—The cycle of this tapeworm is similar to the above, with the pig replacing cattle as the usual intermediate host However,

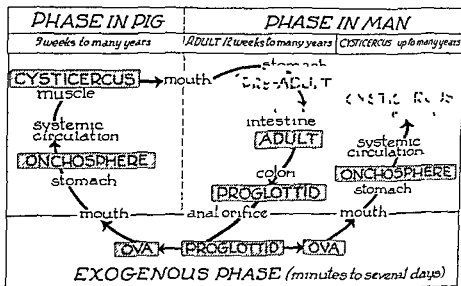


Figure 157 The life cycle of *Tænia solium* (The possible endo auto-infection is not shown in this diagram)

that man may also function as ted by man, from another host, *of his own adult worm*, or by endo-auto-infection brought about by reverse peristalsis, so that the proglottids or eggs reach the stomach where the covering is digested off and the ... almost

Diphyllobothrium latum—There are many definitive hosts of this worm other than man—the domestic pig, the domestic dog and cat and other canines and felines, walruses, seals, sea-lions, minks and bears *The* eggs, which are golden-brown in colour, ovoid, 45 by 70 microns contain *immature larvæ within a thin shell*, and have an opening at one pole covered by a cap, are passed in the fæces (figure 158) In water these mature within fifteen days and the embryos (coracidia) emerge, these are

ciliated and swim freely in the water up to 12 hours, after which they would die if they were not ingested by a copepod (crustacean) of certain species of the genera *Diaptomus* and *Cyclops*. They develop in these for two to three weeks and when the crustacean is swallowed by fish these embryos develop into plerocercoid larvæ, long white larvæ measuring up to 6 millimetres, in the flesh (muscle) of the fish. The small fish that eat the crustaceans are later eaten by larger fish such as pike, perch, trout and other fish commonly eaten by man (and other definitive hosts), and in the human intestine these larvæ develop into adult tapeworms in about six weeks. This species grows to a length 10 metres or more, and may have as many as 3000 proglottids. The eggs are evacuated into the intestinal canal from the mature proglottids, which do not separate as in the case of the other tapeworms but atrophy after they have discharged their full egg load. These worms may produce as many as a million eggs a day, but they usually evacuate their eggs periodically, about every third day, for about a month. The eggs are passed out with the fæces and the cycle is complete.

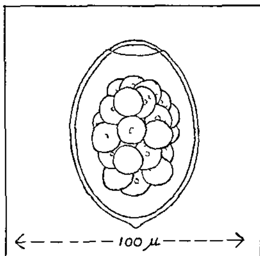


Figure 158. The egg of *Diphyllobothrium latum*

EPIDEMIOLOGY

These infections occur amongst meat-eating and fish-eating persons in many countries but are particularly common amongst groups who eat their food raw or only lightly cooked and in countries where pigs have easy access to human fæces which they will readily eat, or cattle graze in pastures which are frequently contaminated by or deliberately manured with, human excreta.

A number of cysticercus infections in British soldiers who have been stationed in India has been reported [illegible]

The fish tapeworm infection appears to be extending in the United States, several fresh endemic foci have been identified and infected fish is sometimes sent to market in distant towns.

PATHOLOGY AND SYMPTOMATOLOGY

In none of these infections do the adult worms or the excysted larvæ ordinarily invade the host's tissues, but they deflect a certain amount of the host's nutriment to their own use, and secrete substances which may

act as toxins or allergins Rare instances of the scolices having penetrated the intestinal wall and caused peritonitis have been reported And finally the cysticerci of *T solium* may develop in man, as they do in the usual intermediate host in any tissue or organ of the body As the pathogenesis and symptoms produced by each of the two stages of the worm are of an entirely different order from those produced by the other, it will be advis able to describe them separately

The adult worms—The symptoms produced are irregular and ill defined Loss of weight indigestion and general abdominal discomfort and in allergic individuals periodic diarrhœa may occur All somatic symptoms may be absent, especially in *T saginata* infection but the host may be reduced to a state of neurasthenia by knowledge of the presence of the worm, and by the embarrassment caused by the emerging segments which may appear at unexpected moments on the host s stockings or shoes In *D latum* infection, however, there is in certain cases evidence of some intoxication produced by the metabolites of the worm A macrocytic anæmia of the pernicious anæmia type has for many decades been asso ciated with this infection Although the work of Birkeland (1932) seemed to cast doubts on the causal relationship between the infection and the pernicious anæmia that is very prevalent among Finnish nationals more recent work seems to support the suggestion that the worms metabolites which are of the nature of unsaturated fatty acids are capable of producing anæmia (Wardle and Green 1941) Anæmia has not been reported in Canadian and North American cases

The cysticerci of T solium—The onchospheres having reached the blood stream migrate into the tissues in any part of the body, but appear to have a preference for the brain, the muscles and the subcutaneous tissues Here they give rise to a tissue reaction and are eventually surrounded by a fibrous capsule of host origin Within this rigid host capsule the cys ticercus continues to develop the parasitic wall of the cyst becomes folded upon itself and in some cases produces a relatively large 0 5 to 1 centi metre racemose cystic growth There is apparently a stage at which a balance between host and parasite is reached and no further development takes place for several years, but, when the parasite dies this symbiosis is disturbed the capsule becomes permeable and fluid enters and toxin escapes so that there is renewed tissue reaction and an increase in the size of the parasitic mass at least temporarily Later, there is either calci fication or the foreign body is partly or completely removed The life of the cysticerci is probably very variable but it is probable that they live for at least three years and after their death at least another three years elapses before they become calcified

The symptoms depend on the site in which the cysticerci are located and of course on the number present A heavy invasion may be asso ciated with pyrexia other general symptoms of a toxæmic nature and pres sure symptoms if vital tissue is involved Generally however the symp toms are postponed until the worm dies when further pressure and toxæmic symptoms may appear The symptoms associated with the foreign body effect of the cysticercus in the tissues frequently do not develop until the worm is dead and calcification has occurred

The sites where they are most usually reported are (i) in the subcu taneous tissues where they form lumps that are clinically recognized (ii) in the brain where they produce a number of symptoms from mild mental changes such as deterioration of memory to Jacksonian epilepsy and total

mental degeneration and are recognized by x ray examinat the eyes where they may actually be seen in the anterior chamber, (iv) and in other tissues such as the muscles, tl recognized accidentally during x ray examinations or post mor

There have been reported several instances of the simil ment in man of the plerocercoid (sparganum) larval form of Bc loidea, probably not of the species *Diphyllobothrium latum* b species such as those that live in lower vertebrates, these m mild or severe symptoms according to the site in which the The condition is sometimes known as 'sparganosis'

DIAGNOSIS

In tænia infections this will usually depend in the finding of the proglottids in the stools or on their presence being reported by pa tients and in *D latum* infection by the finding of the eggs in the stools

In *T solium* and *T saginata* infections eggs will occasionally be found in the stools but this finding must not be expected The eggs are practically identical and for differentiation one must rely on examination of the mature or gravid proglottids This can be done by flattening them out on a slide placing a coverslip over them examining the uterus and counting its primary lateral branches in *T solium* there are 7 to 13 primary branches and in *T saginata* 15 to 20 (figure 159)

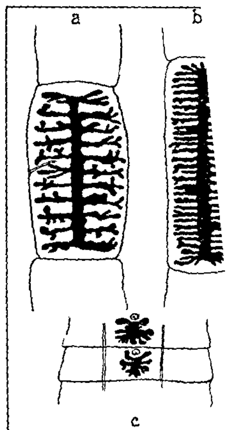


Figure 159 Tapeworm proglottids
a *Tænia solium*
b *T saginata*
c *Diphyllobothrium latum*

After unsuccessful treatment that leaves the scolex *in situ*, proglottids will usually reappear in the stools within three months

On the other hand the eggs of *D latum* may be found in the stools but a number of examinations will have to be carried out before a negative diagnosis can be made as the extruded by the worm intermittently In this infection proglottids not usually found in the stools in an untreated case the net from the other two being m... almost stellate ...

The presence of **cysticerci** may be diagnosed by the palpation and/or *removal of the tumours* in the subcutaneous tissue or muscles, by the symptoms they produce, when they occur in vital tissues or by x ray examination The x-ray examination requires special experience, the exposure should be that given for bone visualization with a slight under exposure The opacity may be produced by a calcified scolex *one millimetre in diameter or by a fully* developed cysticercus as large as two centimetres in length It will seldom be worth taking a skiagram within 6 years of the probable time of infection

It has been said that whenever epileptic fits occur in an adult without a history or injury or a family history of epilepsy cysticercosis should always be suspected

PREVENTION

If the beef, pork, and fish are properly cooked the cysticerci will be destroyed (65 5° C is lethal) and direct personal prophylaxis achieved

As a measure of general prophylaxis, in most countries meat is inspected In the United States, two thirds of the beef that is consumed by the public is inspected In 1930, 0 37 per cent of carcasses were found infected and were condemned, the figure has improved in recent years *Pork is similarly inspected and 'measly pork' discarded*

It is possible to go one stage further back in the matter of prophylaxis and to prevent cattle from grazing on pasture contaminated with human fæces, or pigs from eating human fæces Regulations to achieve this will be difficult to enforce, but if meat and pork are inspected frequently and when found infected condemned, and the cause of their meat becoming infected is explained to farmers, the economic aspect will probably appeal to the cattle and pig raisers in the sanitary advanced western countries and they will take the necessary steps However, in eastern Europe, and in Asia where pigs and cattle are allowed to roam freely, the prevention will be much more difficult

In the case of *D latum*, though there are many other definitive hosts man is believed to be the most important and the prevention of the sewage contamination of water where edible fish are caught will be an effective preventive measure

Cysticercosis cellulosæ is prevented by the immediate and thorough treatment of all infected individuals, and by observation of rigid personal hygiene, especially by those who know that they are infected In certain circumstances, isolation of the infected individual would be justifiable

TREATMENT

Male fern has been the specific for this infection for many years but some improvement has been effected recently in the preparation the standardization, and the method of administration of this drug

An unopened bottle of the oleo resin of *Aspidium filix mas*, or better still gelatin capsules containing 10 or 20 minims each of this drug are obtained The patient is given two ounces of saturated sodium sulphate [illegible] morning on an empty stomach at 7 00 7 30 and [illegible] venient) one 20 minim capsule (or two [illegible] dose of 60 minims *Two hours later*, [illegible] food is withheld until the patient has passed a copious stool, which will contain the whole or most of the worm

The dose for young **children** is a total of two minims for each year of *apparent* age For children of over 100 pounds in weight 25 minims, for children of 150 pounds and under sized adults 45 minims, and for children over 170 pounds the full adult dose of 60 minims is given, this total dose is divided into three equal parts each of which is given in a teaspoonful of sugar

This dosage will effect a cure in about 80 per cent of cases If a patient is in hospital, the stools for the next 48 hours should be kept, screened and the debris examined for the scolex If this is not present, the treatment may be repeated in a week On the other hand if the patient is at home, it is a mistake to insist on his keeping and searching his stools, as the procedure is very distasteful and is not likely to be done effectively If he is not cured he will know in due course, in either of the *Tænia* infections, if the scolex is not removed proglottids will be passed again in two to three months time and the case of the fish tapeworm there will be a return of eggs to the stools within five or six weeks

A method of treatment that is undoubtedly very satisfactory from the point of view of the physician is that practised by Dr J S D'Antoni of the Tulane School After a preliminary saline purge, he gives by duodenal intubation the following mixture —

Oleo-resin of male fern—one drachm
Saturated solution of sodium sulphate—one ounce
Mucilage of acacia—one ounce
Water—two ounces

No further medication is necessary and within an hour the whole worm, usually intact, will be passed One hundred per cent success can be expected

Of the other drugs, carbon tetrachloride is the best and after this ... ifer for persons not under hospital ... not have to be prohibited The ... treatment of hookworm infection ... (1943) obtained an 80 per cent cure rate with the former and 54 per cent with the latter These drugs are less satisfactory from the point of view of the helminthologist because the worms are often disintegrated when passed but they are cheaper, easier to obtain, less unpleasant to take, and probably safer than oleo resin of male fern It seems very probable that by intubation they would be as efficacious as is male fern by this route

... Any anæmia as... m a hæmato- lo... a macrocytic ty... l liver extract either by mouth or parenterally will be indicated

Cysticercosis cellulosæ—*No specific treatment appears to have any* beneficial effect on the pathogenesis This is to be expected as most of the pathological changes are associated with the death of the worm Surgical removal is practicable in certain circumstances

PROGNOSIS

In infections by the adult tæniæ, the prognosis is excellent, but in *T solium* infection the danger of auto-infection must be explained to the patient In established cysticercal infections, however, the prognosis must

always be guarded, as localization in the brain is very common, and may not become evident for many years

Generally, the prognosis in *D latum* infection is also good, and even the severe anæmia that develops in some subjects is easily curable, at least in those who have no background of pernicious anæmia

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THE DWARF TAPEWORMS

Geographical distribution.—Both these tapeworms are cosmopolitan in their distribution but *Hymenolepis nana* shows a patchy distribution, with here and there hyper endemic areas, *e g* in India and Argentina, for which there is no obvious explanation *H diminuta*, of which the rat is the true definitive host, has been reported in man, mainly in India, Russia, Japan, Italy, and the southern United States

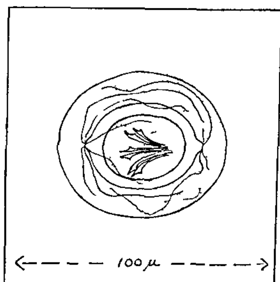


Figure 160 The egg of *Hymenolepis nana*

ÆTIOLOGY

Both dwarf tapeworms have the same general morphological characters as the large tapeworms

Life cycles and morphology ***H. nana*** —The eggs are sub spherical, 30 to 45 microns in diameter, they have an outer vitelline membranous covering and an inner shell with small projections at the poles from each of which arise 4 to 8 filaments and they contain an onchosphere with three pairs of hooklets (figure 160)

An egg is ingested by man, and after passage through the stomach ... llus in the small intestine where ... or 6 days, this larva migrates ... to the mucous membrane, and develops into an adult (25 to 40 mm in length with a maximum breadth of 1 mm) *From the time of ingestion of the egg, the adult worm becomes* mature in about two weeks, and when it is mature the terminal proglottid disintegrates and releases about 180 eggs into the intestinal canal Normally these are passed out with the stools and the cycle is completed, but there is strong evidence that they may hatch in the intestinal canal (whether for this to occur it is necessary for them to be returned to the stomach by reverse peristalsis is not clear), and by a process of endo-auto infection again go through the whole developmental cycle in the same individual Reinfection by the external route also occurs

H diminuta —*The egg is similar to that of H nana,* it is subspherical, 60 to 80 by 72 to 86 microns, but has a slightly thicker outer covering and no filaments between the two membranes (figure 161)

The egg is ingested by an arthropod intermediate host (a large variety, from grain moths earwigs cockroaches and millepedes to flea larvae, have been incriminated where it develops into an onchosphere and finally a cysticercus in due course the arthropod is ingested by man or other definitive hosts e g rodents in whose intestine it develops into the adult worm (20 to 60 cm in length with a maximum breadth of 4 mm) The mature terminal proglottid disintegrate and release the eggs which are passed out with the stools

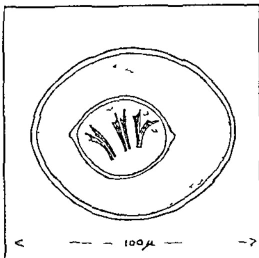


Figure 161 The egg of *Hymenolepis diminuta*

EPIDEMIOLOGY

Man is probably the only important source of *H nana* infection it usually is a family household or institutional infection Children show the highest incidence In the United States eggs are found in about one per cent of all stool specimens in Calcutta a slightly higher infection rate was found and in Argentina a 9 per cent infection rate amongst a group of children has been reported

H diminuta is relatively rare and is usually associated with low sanitary standards where murine parasites and other arthropods may be accidentally consumed with food Infection has occurred through the consumption of insects infesting prepared cereal foods (Chandler 1922)

PATHOLOGY AND SYMPTOMATOLOGY

H nana invades the mucous membrane during its larval stage secreting toxins and allergins and heavy infections cause a considerable degree of toxæmia which are clinically manifested by convulsions giddiness and even epileptiform attacks Abdominal discomfort is a common complaint and watery diarrhœa possibly of allergic origin is sometimes associated with this infection

There is usually a moderate degree of eosinophilia up to 16 per cent

H diminuta infection is not usually associated with any symptoms

DIAGNOSIS

This is made by the identification of the characteristic eggs in the fæcal smear or by the concentration technique (*see* p 620) or after anthelminthic treatment—possibly for other worm infections—by the finding of the whole or part of an adult worm in the stools

PREVENTION

Improvement in general sanitation and personal hygiene are indicated As auto infection is common special attention must be paid to hand wash

ing after stool and before meals *Treatment will also be an important measure, every infected persons in a household or institution must be treated*

TREATMENT

The treatment of *H nana* infection is complicated by the fact that both auto-infection and re-infection are common It is therefore advisable

TABLE XVIII

DIAGNOSIS AND TREATMENT OF INTESTINAL HELMINTHS

Worm	Incubation period weeks	FINDINGS IN FÆCES		Eosinophilia	Drug or drugs of choice and adult dose
		Stage	Constancy		
Ascaris lumbricoides or round worm	8	egg	numerous	+ +	Oil chenopodium—1 c cm *plus* tetrachlorethylene—3 c.cm or Hexylresorcinol—1 gramme
Trichuris trichiura or whipworm	12	egg	numerous	+	Leche de Higuerón—2 ounces or Hexylresorcinol—1 gramme or tetrachlorethylene—3 c cm
Enterobius vermicularis or threadworm	8	egg	scanty*	+	Gentian violet—1 grain x 3 for 8 days followed by second similar course after 7-day interval
Ancylostoma duodenale or hookworm	5	egg	numerous	+ +	Tetrachlorethylene in 4 c cm in saturated sodium sulphate—1 oz or *Hexylresorcinol*—1 gramme
Strongyloides stercoralis	4	larva	irregular	+ + +	Gentian violet (enseals)—1 gr x 3 for 17 days
Trichostrongylus	(5)	egg	constant	+ +	as for hookworm
Tænia solium or pork tapeworm	6–12	proglottid	irregular	+ +	Filix mas—20 minims x 3 in gelatin-coated capsules by mouth or 60 minims in saturated sodium sulphate by duodenal tube or carbon *tetrachloride*—3 c cm
Tænia saginata or beef tapeworm	10–12	proglottid	irregular	+ +	
Diphyllobothrium latum or fish tapeworm	5–6	egg	periodic	+ +	
Hymenolepis nana or dwarf tapeworm	2	egg	periodic	+ +	Gentian violet—1 grain x 3 for one week or Hexylresorcinol—1 gramme

*Found in anal swab

to prescribe an anthelminthic that can be taken over a relatively long period or repeated often Gentian violet meets this requirement best, it is given for one week only in the daily doses recommended for strongyloidiasis (see p 632)

Hexylresorcinol is also a benign drug that can be repeated It will be advisable to give this in the doses advocated for ascariasis (see p 599), but it should be given twice with a one week interval

In view of the fact that a multiple infection may arise in an individual from the infection by a single worm by means of auto-infection, even if re infection can be excluded complete eradication of the infection must be achieved If no eggs are found at weekly examinations over a period of one month cure may be assumed

For the treatment of *H diminuta* infection, provided the source of infection has been eliminated, a single efficient treatment will be sufficient Either of the above drugs could be used, but the oleo-resin of *Aspidium filix mas* is considered to be more specific

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TRICHINOSIS

Introduction—Trichinosis or infection with the worm *Trichinella spiralis* (Owen 1835) Failliet 1895 is in no sense a tropical disease The geographical distribution in fact indicates that a warm climate has some inhibitory effect on the infection, as it is more common in the northern

than the southern United States and is apparently absent from large areas in the tropics where it is hard to account for its absence on dietary considerations alone

prevalent there

The public health importance of the d sea e has been fully recognized for at
reaks in the Un ted
revalent in both of
(1943) have shown

EPIDEMIOLOGY

Geographical distribution —Published data probably give a poor idea of the real distribution but it is certainly prevalent in Great Britain (Sheldon 1941) in many European countries and in the United States (from Boston in the north 27 6 per cent to New Orleans in the south 3 5 and 6 per cent) Cases have been reported from Kenya Uganda and Tanganyika and from Brazil and Chile but evidence that it occurs elsewhere in Africa in Asia or in Australia is absent In India Maplestone and Bhadhuri (1942) reported finding *Trichinella spiral s* in a single cat after failing to find it in 100 dogs 100 pigs 100 rats and 73 cats whose diaphragms were examined specifically for this infection by the digestion extraction technique and after a study of the literature for the preceding 75 years they could find no records of the infection in man or animals in that country

Distribution in population groups —For all practical purposes the flesh of the pig is man s only source of infection and the investigations of Wright and his colleagues (*loc cit*) only showed the infection in one of the two hundred Jews included in their investigation The infection rate and clinical evidence of the disease is more common in country than in town populations There are two factors here—the better inspection of the pork in the cities to account for the lower infection rate and the lack of concentration of infected material as would be likely to occur in the country when a heavily infected pig would probably be distributed to a few families only to account for the lower morbidity rate in cities

Sex —In several populations the infection rate has been found higher in women than in men This has been accounted for by the practice of eating uncooked sausage meat in particular that is apparently common amongst women in these populations

ÆTIOLOGY

matode worm
nm in diam
100 microns

Hosts —The cycle can be completed in one host species but two individuals are necessary The common hosts are pigs dogs cats and rats and in certain countries bears but any carnivorous animal may be infected

Rats, which are cannibalistic, are probably the most important reservoir of infection and the pig is the important source of infection to man, although many fatal infections have been acquired from bear meat Man is only an incidental host and under normal conditions constitutes a *cul de-sac* for the parasite

The life cycle —Encysted larvæ are ingested the gastric juice digests the cyst wall sufficiently for the larvæ to escape in the duodenum They penetrate the mucosa superficially and in from five to seven days develop into adults The worms mate probably in the crypts the male dies and is passed out with the fæces, and the female again burrows deeply into the mucosa and parturiates producing 1500 larvæ over a period of about six weeks The larvæ penetrate the lymphatics and venules and eventually reach the systemic blood stream and come to rest in striped muscle They appear to prefer muscles such as those of the diaphragm intercostal spaces tongue, larynx and abdomen that are constantly active (the low glycogen content appears to be the factor, as insulin increases and glucose decreases the number of larvæ that will encyst), but they will also encyst in certain skeletal muscles (e g the biceps), and rarely in other organs and tissues A boat shaped fibrous capsule is formed around the larva within which it grows to about one millimetre in length and lies curled up (figure 162) The host is then eaten by another carnivore and the cycle is complete (figure 163)

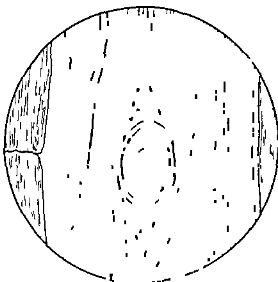


Figure 162 Encysted larva of *Trichinella spiralis* in human muscle

Man may take the place of the host but in this case the cycle will not ordinarily be completed

Immunity —There is evidence that rats acquire an immunity to subsequent infection after the first infection incident Actual proof that this is so in the case of man is want why the morbidity rate is so low, in only those who received a heavy do *first* exposure would show any morbidity However, larvæ of apparently different ages have sometimes been found in one individual

PATHOLOGY

The pathological changes produced in man by this infection can be conveniently divided into three phases The first phase includes the period of invasion of the infecting larvæ, their development into adults their mating and the subsequent re entry of the female into the mucosa This may cause a considerable reaction in the mucosa with cellular infiltra

tion œdema some necrosis of the superficial layers of the mucous membrane possibly a little hæmorrhage and considerable outpouring of fluid into the intestinal canal

The second phase commences with the parturition of the female the migration of the larvæ through the tissues their destruction in some tis

the larvæ

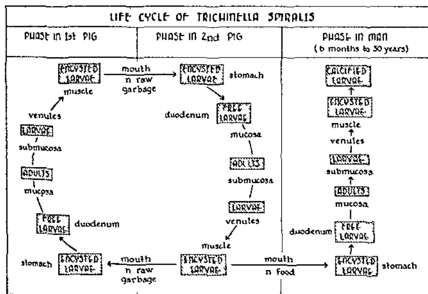


Figure 163

This boat shaped capsule containing the curled up larva lies between the muscle fibres with its long axis parallel to them Some changes are evident in the surrounding muscle swelling of the muscle fibres proliferation of interstitial tissue or in some cases degeneration of the muscle fibres

In other tissues in which the larvæ are not able to encyst for example in the myocardium and the central nervous system there is evidence that they will nevertheless migrate and cause a very considerable cellular and inflammatory reaction to their toxins', which leads to the destruction of the larvæ, and not infrequently in severe infections to the death of the host

The third phase is a quiescent one cysts will remain viable for a

Blood picture—The eosinophil count is constantly high except in debilitated subjects It may rise to 6 000 per c mm (over 60 per cent) in the acute stages, but it will tend to decrease later, however, an eosinophil count of 1 000 per c mm or more may be found in an infected subject for several years

SYMPTOMATOLOGY

The severity of the clinical picture will vary almost exactly with the weight of the infection, and the vast majority of infections are light and symptomless throughout On the other hand, there are a few cases in which certain grave symptoms can undoubtedly be traced to cardiac and cerebral involvement in heavy infections, these rarer clinical manifestations will not be described here

It is convenient to consider the clinical course as being divided into three stages that correspond roughly to the three phases of the pathological picture Firstly, there is the gastro-intestinal stage which may commence within twenty-four hours of the ingestion of the infected meat and last for several days often overlapping the second stage This first stage corresponds to the period of activity of the larvæ and adults in the mucosa of the duodenum and probably ends when the female penetrates more deeply and commences to parturiate

The second or the toxæmic stage, characterized by œdema swellings and pyrexia, and later by hæmorrhages, pain in the muscles and other localizing symptoms, commences on the seventh to the tenth day with the parturition of the female and lasts as long as she is discharging larvæ it covers the period of destruction of the larvæ in unsuitable tissues and their encystment in suitable ones, a period of perhaps six weeks The subdivision of this stage into two periods that is frequently made in the literature seems to the writer artificial, as the phase in the life of the parasite is a continuous one

The last is really the convalescent stage, in which the patient is recovering from the effects of the toxæmia, but may have some residual disabilities as a result of the presence of encysted and possibly calcified larvæ

The gastro-intestinal stage—It is apparently only in very severe infections that this stage is prominent In such cases there is severe watery diarrhœa often with vomiting *so that the condition may simulate cholera*

days earlier, but in the majority constipation will be reported

The toxæmic stage—The most constant and prominent symptom is swelling of the eyelids The patient may wake up in the morning with the eyes completely closed and even with *the œdematous conjunctivæ* everted and bulging The rest of the face may also be swollen and there may be swellings in other parts of the body The conjunctivæ are usually injected

The temperature is almost constantly raised, usually up to 101° or 102° F, and there is often a remittent type of temperature lasting for one, two or three weeks, or even longer

There is *sometimes urticaria*, and other rashes have been described

As well as severe frontal headache, which is another very constant symptom, lethargy and apathy or anxiety and irritability have been observed in a considerable percentage of cases. Areflexia is frequently observed.

Cough is common and hæmoptysis occurs rarely.

About the third day after the swellings have appeared there will often be pain in the various muscle groups, so that breathing becomes laboured, and mastication and deglutition difficult, and in fact all muscular movements, particularly after a period of rest, are painful. Pains may be slight or very severe, and are often described by women as being as intense as labour pains. They may last for one day or for several weeks.

In this stage, if the fever continues for a month or so there will be considerable emaciation and very great weakness with nervous and mental symptoms that suggest the typhoid state.

A somewhat unusual symptom, hæmorrhages under the nails and extreme tenderness of the tips of the fingers, has been noted in about ten per cent of clinical cases.

In fatal cases, death takes place during this second stage.

The final stage.—In this stage the patient recovers from the weakness and emaciation of the toxæmia and fever. There are often residual pains and muscular pains that may persist for many months and muscular weakness that may last for years. Calcified cysts can seldom be felt but can be seen by careful radiography.

DIAGNOSIS

This will have to be considered under four headings (a) clinical and epidemiological, (b) parasitological, (c) immunological and (d) post-mortem examination.

(*a*) **Clinical and epidemiological.**—A clinical diagnosis is unlikely to be made unless there is an epidemic or the patient gives a clear history of having eaten raw or insufficiently cooked meat that he suspects, but in either of these cases the swelling of the face in the absence of any renal or cardiac cause, the febrile attack in the absence of any demonstrable infection, and the severe cramps in the muscles in the absence of dehydration and hypochloræmia will be highly suggestive. A high eosinophil count without any other apparent cause will add support of this diagnosis.

(*b*) **Parasitological.**—Only by a very unlikely chance will the adults or the larvæ be found in the stools or the latter in the blood or other fluids, *e.g.* cerebrospinal fluid, but the search for encysted larvæ in muscle biopsy specimens is a useful method of diagnosis, as many as 800 larvæ per gramme have been recovered from non-fatal cases. The piece of muscle can be examined pressed between the slides, or after digestion in artificial gastric juice for 24 hours at 37° C. (*vide infra*).

(*c*) **Immunological.**—The intra-dermal test has been used widely for [illegible]

Techniques The antigen* is prepared from desiccated larvæ extracted fro infected pork

which 0.2 c cm of at least 7 mm ounded by a rin

A control in which the solvent is used without any antigen must be done a the same time

The delayed reaction which may occur after a delay of 24 hours is less specific

The **precipitin test** is done with dilutions of 1 in 100 upwards of the sam antigen In a micro-tube a small quantity of the antigen solution is floated on top of an equal amount of the patient s serum and the reading is made after one hou in the 37°C incubator A positive result in a dilution of 1 in 1250 or more suggest recent infection

These tests become positive between the second and third weeks and remain positive for several years

(d) **Post-morten examination** —The diaphragm is usually the best source of trichinella larvæ A piece of this is cut into a thin slice which is pressed between two strong slides and then examined under the low power lens of the microscope for encysted larvæ

A more satisfactory method is by digesting the muscles as follows

Technique Digest about 50 grammes of muscle in 0 7 per cent hydrochloric acid—1.0 per cent of pepsin 20 c cm to a gramme of muscle overnight The mixture should if possible be stirred periodically The digested material is placed in a large glass funnel to which a short length of rubber tube with a stop-cock is attached The encysted larvæ fall to the bottom of the funnel and can be drawn off by opening the stop-cock A count can also be made by th s method

PREVENTION

P … om eating lightly cooke … or 24 hours will destro … noking will not

T … practised is the inspec … the fact that tion is adequa of the value of this procedure

Education and propaganda amongst small pig raisers in country districts to discourage raw garbage feeding and to encourage the proper disposal of pig viscera and of the carcasses of pigs dying of disease is important Rats also being common hosts should be destroyed or at least kept away from the animal food store

TREATMENT

No specific for this infection is known and from the nature of the infection and the difficulty of early diagnosis it seems doubtful whether a specific would be of very great value were one discovered unless it were capable of killing the encysted larvæ in the muscles Treatment must therefore be symptomatic and palliative

The administration of calcium, in the form of calcium gluconate for example has been suggested in order to hurry the encapsulation of the larvæ

* Prepared antigen can be obtained from Eli Lilly and Co and probably other drug manufacturers

PROGNOSIS

It must be obvious that the prognosis in the vast majority of cases is excellent as they do not show any symptoms at all On the other hand in the very heavy infections in which gastro intestinal symptoms appear the prognosis should be guarded as many deaths have been reported In such cases the absence of a high eosinophilia is a bad prognostic sign

It has been estimated that 5 000 larvæ per kilogramme of body weight will usually prove fatal However 800 larvæ per gramme of muscle have been recovered by biopsy in a non fatal case The two statements are not necessarily contradictory

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FILARIASIS

FILARIASIS DUE TO *WUCHERERIA MALAYI*

FILARIASIS DUE TO *LOA LOA INFECTION*

ONCHOCERCIASIS

Introduction.—Filariasis* is the term applied to the infections and to the diseases caused by the infections in man and animals by certain nematodes of the super-family Filarioidea that were at one time generally placed in the now superseded genus Filaria, namely

Wuchereria bancrofti (Cobbold 1877) Seurat, 1921
Wuchereria malayi (Brug, 1927) Rao and Maplestone 1940
Loa loa (Cobbold, 1864) Castellani and Chalmers 1913
Mansonella ozzardi (Manson, 1897) Faust 1929

For the other two important infections by nematodes of the super-family Filarioidea, namely,

Onchocerca volvulus (Leuckart, 1893) Railliet and Henry, 1910
Acanthocheilonema perstans (Manson, 1891) Railliet Henry and Langeron, 1912

the words 'onchocerciasis' and 'acanthocheilonemiasis' are commonly used although both worms are often referred to as filarial worms

The morbid changes that occur in filarial infections are brought about by the mature larvae and the adult worms passing through or lodging in the tissues, especially in the lymphatics and causing local reactions

* This section has been written with the aid of some notes by Dr S S Rao especially on the morphology of the parasites, on the history and distribution of [illegible] and on W. [illegible]herena malayi infection Most of the photographs were of his [illegible] department of the Calcutta School of [illegible] cine (May 1944) it is reproduced here [illegible]ion

Ma so ella ozzard is confined to the Amer cas where t has a l m te d d s-

Afr a and in the coastal areas of trop cal and sub trop cal South America The

No further reference will be made to either of these two infections

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FILARIASIS DUE TO *WUCHERERIA BANCROFTI*

filar asis

EPIDEMIOLOGY

Geographical distribution —Of the human filarial parasites *Wuchereria bancrofti* has the most extensive distribution in the trop cs and sub tropics and occurs in reg ons from about 42° N to about 38° S in the eastern hemisphere and from about 30° N to 30° S in the western hemisphere

In **America** the infection is common in Central America in the West Ind es in British Dutch and French Guiana Venezuela Braz l Peru and Colombia In the United States a considerable focus of infection probably originally introduced from Africa was discovered in South Carolina some years ago but no fresh cases have been reported in recent years it probably does not occur elsewhere

It is common on the west coast of **Africa** in Madagascar and the ne ghbouring islands of Mauritius and Reunion in East Africa and in Egypt and North Africa

In **Europe** it is reported to occur in Spain (Barcelona) Hungary and Turkey

ds x ly

In **As a** it is especially prevalent in Arab a India Ceylon Burma the Malayan peninsula the Phil ppines and the islands of East Indies southern China and southern Japan In some of these areas over 80 per cent of the population are infected

In **India** the infection is extremely prevalent but it is more or less confined to the coastal regions and to areas along the banks of the im

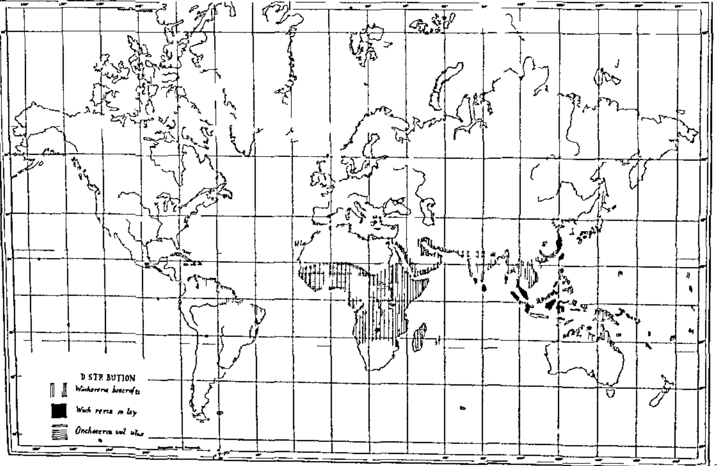


Figure 164 Distribution of Filariasis

portant rivers West Bengal Orissa Travancore, Cochin and Malabar are the most heavily infected areas (microfilaria rate over 20 per cent)

All these are low flat countries that have a high rainfall they are water logged for many months each year and the temperature and humidity are both high for over half the year, conditions are therefore very favourable for the breeding of mosquitoes and for the transmission of the infection The moderately infected region (microfilaria rate between 5 and 20 per cent) include the rest of the east coast of India East Bengal the United Provinces, Bihar, and certain areas in the Bombay Presidency such as Surat, Ahmedabad and Thana Mildly endemic areas include the whole of the Deccan plateau the Central Provinces and Assam However the intensity of infection is not uniform even within a single endemic area, for instance, in Calcutta the eastern wards of the city show a much heavier infection rate than the central or western wards

All the areas lying north of a line drawn from Karachi to Delhi are free from the infection these include the Punjab Sind the North West Frontier Province, Kashmir and Rajputana Elevated regions above 4 000 feet are also free from infection

Epidemic status —It is essentially an endemic disease and any rise and fall in the incidence of the disease will as a rule only take place over a number of years Rises in incidence are usually associated with increases of population or with an increase in the Culex population through ill advised engineering or agricultural undertakings or through a deterioration in the sanitation of the area (*vide infra*) conversely any decline in incidence can usually be traced to improvement in sanitation especially with reference to anti mosquito measures or more rarely to reduction in the human population

In most places the disease has already found its own level so that as occasionally happens when an infected group of individuals from a highly endemic area migrate or are transferred to an area of low endemicity, there is seldom more than a temporary increase in the infection rate in the local population, if any increase at all is noted On the other hand when an uninfected population is transferred to an endemic area the immigrants will in the course of years become infected but their arrival will probably not lead to a general rise in the incidence of the disease in the area as occurs in the case of most epidemic diseases *

Seasonal distribution —In highly endemic areas infection takes place at any time of the year but in the areas of moderate and low endemicity it will only take place at a time when the temperature humidity and other conditions are favourable (*vide infra*) However the time taken for the development of symptoms is so variable and usually so long that the onset of symptoms bears little time relation to infection In Calcutta the highest onset period was during the monsoon July to September there were 40 per cent more fresh cases than in the cooler-weather months October to February But this probably indicates nothing more than a lower resistance on the part of the patient at this time of the year

Race, sex, age, and occupation —No definite relations appears to exist between the incidence of infection and the age or sex of the popula-

*This is the usual experience but when a non infected group lives in close association with a hyper-infected population the intensity of the infection to which they are subjected may lead to a much earlier development of the disease amongst the newcomers

tion

1941)

on the

in hyperendemic areas,* elephantiasis may commence even at as early an age as 5 years, and, in one case, microfilariæ were detected in the blood of a baby of 14 months In moderately endemic areas, the lesions commence generally between the ages of 14 and 16, and in areas of low endemicity between 20 and 25 years In general the incidence of infection in women is less than in men This may be partly due to their conditions of living and their mode of dress

No special correlation between the incidence of infection and the race or occupation of the individual has been noted In Calcutta a town of moderate endemicity, it is very rare for the disease to be found amongst European sojourners but it is not uncommon amongst those who have lived there all their lives, and it is as common amongst the poorer Anglo Indians as amongst the Indians

ÆTIOLOGY

Historical—The discovery of microfilariæ in the hydrocele fluid of a filarial patient was first made by Demarquay in 1863 in Paris In 1866 Wucherer independently discovered a microfilaria in the chylous urine of a filarial patient in

that the filarial embryo dev op

inside the mosquito in seven days In 1900 Low demonstrated that the infective larvæ escaped from the proboscis of the mosquito on to the skin at the time of

researches deal

(Bahr 1912)

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e intermediary

host

James showed that the filarial parasite in Trivandrum developed in *Anopheles subpictus* subsequent investigations especially those of Cruickshank and Wright (1912) and of Iyengar (1932) have however shown that *Culex fatigans* plays a far more important role in the transmission of *Wuchereria bancrofti* than *Anopheles subpictus*

* Endemic areas can for convenience be classed as
 (a) hyper-endemic areas—microfilaria rate 30 per cent or more
 (b) highly endemic areas—microfilaria rate 20 per cent but less than 30 per cent
 (c) moderately endemic areas—microfilaria rate less than 20 but over 5 per cent and
 (d) areas of low endemicity—microfilaria rate 5 per cent or less but an occasional positive finding

Causal organism —The **adult** *Wuchereria bancrofti* are white hair like translucent worms having a smooth cuticle The male and the female worms live coiled together in the dilated lymphatics the male being considerably smaller than the female The head is rounded and is separated from the body by a neck like constriction It is provided with two rows of small sessile papillæ The mouth is without lips and unarmed The œsophagus has no bulb like swelling at its posterior extremity The anus is situated close to the posterior extremity of the worm

Males measure from 25 to 40 mm in length and about 01 mm in breadth The tail is specially curved ventrally The cloaca is about 0 1 mm from the posterior extremity The testis is not coiled and terminates as a snowdrop like process (
which is chitinous is crescen
The long one is cylindrical
ending in a glans like swelli
throughout gutter like and
tremity There are nine pa
five pre anal and four post anal in position The caudal alæ are sometimes indistinct (Maplestone and Rao 1939)

Females measure from 50 to 100 mm in length and from 0 2 to 0 3 œsophagus has no bulb like swelling at its posterior extremity The anus opens about 0 2 mm from the tip of the tail The vulva opens on the ventral surface about 0 6 mm to 1 3 mm from the anterior end The
and
with
the
the
inch
of the uterus contains eggs and embryos in various stages of development

The ova and embryos —The ova are found in the posterior end of the uterus Their dimensions vary according to the stage of their development when fully developed they measure about 40 microns in length and 25 microns in breadth The ovum does not possess a true shell but only a membrane which becomes stretched to form the so called sheath of the microfilaria

is 359 microns (Iyengar 1939)

The embryo shows well marked cuticular striations The cephalic space is generally smaller than the breadth of the embryo in this region The tail tapers gradually to a rounded tip and is free from nuclei

* Microfilarial periodicity The maximum number of microfilariæ is found between the hours of 10 P M and 2 A M and never during the day This periodicity is a device on the part of the filarial worm (or of Nature) to aid propagation of

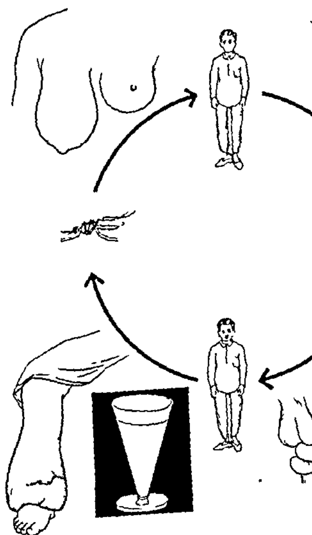


Figure 165 Showing cycle of transmission and indicating produced (including chyluria)

Fiji, Samoa, and other Pacific islands where they show no special periodicity They do not develop further in the blood, but are taken up by the intermediate host the mosquito, where the next stage of development occurs

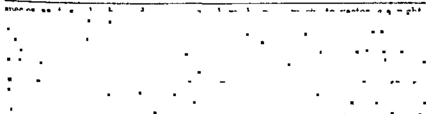
Ordinarily, a drop (20 c mm of peripheral blood of an infected individual may contain anything up to 600 embryos It has been found that, while a moderately high concentration (about 15 embryos per drop of blood) is necessary for the successful transmission of the infection, a much higher concentration of microfilariæ, *viz*, 100 or more embryos per drop, is fatal to the mosquito

The development of the filarial embryo in the intermediate host, the mosquito, may be briefly described as follows

As the mosquito feeds on the blood of an infected individual, the embryos (microfilariæ) are taken in by the mosquito and enter its stomach With the progress of digestion in the stomach, the blood plasma becomes thickened At this stage the embryos escape from their sheaths and enter the thoracic region of their mosquito host It has been shown by Iyengar (1939) that within ten minutes most of the embryos enter the thorax and lie in between the thoracic muscle fibres, where at first they are comparatively inactive After two days the first larval stage embryos measure about 124 to 250 microns by 10 to 17 microns Many changes take place in the structure of the embryos, and the tail becomes reduced to a stump (sausage stage) After the third day, the development of the body cavity œsophagus and the anus takes place and at the end of seven days the larvae (second stage) measure 225 to 300 microns by 15 to 30 microns Caudal papillæ are now observed

During the second week, moulting occurs and under optimum conditions the metamorphosis is complete by the tenth or eleventh day The infective third stage (filariform) larvae which now measure 1500 to 2000 microns by 18 to 23 microns show an alimentary canal and a tri-lobed tail They leave the thorax migrate to the proboscis, and eventually reach the interior of the labium They are generally seen to move in pairs When the mosquito feeds, the larvae escape at the junction of the labium with the labella (figure 166) and enter through the puncture made by the mosquito or even through the unbroken skin

The larvæ find their way into the peripheral lymphatics Their subsequent progress and eventual fate will depend to a great extent on the host s reaction, but under conditions of perfect symbiosis the cycle will be completed as follows The larvae migrate centripetally and eventually reach the large lymphatic trunks where, having developed into male and female adults, they mate The female parturiates and the microfilariæ are



If the host changes his habits and sleeps during the day, the microfilariæ that he harbours will change their periodicity correspondingly in about three days

carried *via* the lymphatic trunks into the subclavian veins and the systemic circulation

This is the outline of the cycle as it occurs when symbiosis is perfect and it accounts for none of the pathogenesis associated with the infection when the host s tissues react to the presence of the worm, these reactions and their effect on the cycle will be described below under the heading of Pathology

It is, however possible that in some instances after the adult worms have mated they, or at least the females migrate centrifugally to the lymphatics of the extremities and genitals to parturiate This hypothe



Figure 166 Infective larvæ emerging from the lip of proboscis of *Culex fatigans*

sis—for which there is analogy but no experimental proof—would help to explain certain observed phenomena though it is believed that these can be explained almost as well on other grounds (*vide infra*)

From the entry of the mature larvae to the appearance of micro filariæ in the blood of the host the interval is usually stated to be about one year but there is evidence that it may be much longer

Correlation between filarial infection and filarial disease—It is no longer necessary to discuss this from the point of view of establishing the [illegible] the various clinical mani [illegible] one of historical interest [illegible] of filariasis are concerned

Many of the early workers *e g* Low (1908) and O Connor (1923), noted the correlation between the incidence of filarial disease and the blood

microfilaria rate *in the community* and recently Iyengar (1938) found a positive correlation coefficient of +0 7644 between the microfilarial rate and filarial disease in 216 localities in Travancore (India) In chyluria due to filarial infection microfilariæ are usually found in the peripheral blood Ray and Rao (1938) found them in 78 per cent of their cases

On the other hand most (though not all) observers have found a very definite negative correlation between blood microfilarial findings and elephantiasis *in the individual* In India Acton and Rao (1930) found microfilariæ in only 5 7 per cent of cases of frank filarial elephantiasis whereas they found them in 14 7 per cent of the symptom free population of the same area In a population in which there was a 92 8 per cent filarial disease rate Rao (1941) found a microfilaria rate of 8 4 per cent in those

elephantiasis

The absence of microfilariæ in the early stages of the infection must be attributed to the immaturity of the filariæ and/or to their failure to mate The usual explanation for the lower microfilaria rate among subjects with

[illegible] can mate more easily [illegible] finding of an occasional pregnant

all the larger lymph channels from the periphery in order to explain the absence of microfilariæ in the peripheral blood it is possible that one must visualize a general reaction of an allergic or an antibody* nature on the part of the host otherwise one would expect the worms in those areas where the blocking was as yet incomplete to provide some microfilariæ Each of these three alternatives is compatible with the observation of Iyengar (1933) that the longer the duration of the obstruction the lower the microfilaria rate is likely to be

Conditions favourable to the development of the larvæ in the mosquito—The stages of the development of the larvæ of *Wuchereria bancrofti* in mosquitoes outlined above require a mean atmospheric temperature of about 80° F and a humidity above 60 per cent Laboratory controlled experiments by Rao have shown that the development of the larvæ in the mosquito depends directly upon temperature and humidity the optimum conditions for the development have been found to be a combination of 80° F *with 90 per cent humidity* Under these conditions the parasite is found to complete its full development in the mosquito within seven days Observations carried out in India (Calcutta and Cuttack) and in China have shown that the times for development in the mosquito under natural

* [illegible] that are retained in the tissues behind [illegible] in the subcutaneous tissues are actively [illegible] tizing (*sensu lato*) stimulus, whereas in [illegible] reach the blood stream where they circu[illegible] they are obsolete and are subjected to a gradual process of absorption with other circulating debris

it is converted into a mass of granulation tissue *and no longer contains* any lymphoid tissue (figure 167) As the lymph channels are obstructed by this granulation tissue, lymph can no longer percolate through the node, nor can the larvæ pass through it, they are held up distally to the obstruction *and there complete their development* In some instances, adult worms fail to mate and the sterile female, after living in the lymphatics for some time, and causing periodic reactions, eventually dies and is absorbed or calcified In others, the adult worms mate and the female parturiates, in *this* sub-optimal environment With the discharge of the embryos, the uterine fluid—which is expelled at the same time—acting as a toxin, causes

Figure 167 Section of lymphatic gland showing sections of filariæ in two lymph spaces

lymphangitis and/or **lymphadenitis** (In sections of tissue containing worms, a large number of desquamated endothelial cells derived from the endothelial lining of the vessel walls can sometimes be seen at the site of *the vulval orifice of the worm*, which is close to the head end) In this way an obstruction is gradually formed to the centripetal flow of the lymph and the pressure rises in the obstructed lymph channels

[illegible] birth to living embryos intermittently, prob- [illegible] e most likely explanation [illegible] allergic signs and symptoms, both local and general When the gravid female ceases to produce embryos, toxins are no longer excreted to the same extent as during fecundation and, for the time being, the inflammation subsides

The primary factor in the mechanical production of lymph varices is this intermittent rise and fall of the lymph pressure Clinically, such varices are seen most frequently in lymphatics *that are supported by* loose

tissue such as those around the superficial lymph nodes on the inner aspect of the arm etc or when the deeper lymphatics are involved the abdominal plexuses and those of the spermatic cord (*vide infra*)

The local reaction to the presence of a foreign body in a lymphatic vessel or in a lymph node may be such that the mature worm or even the



Figure 168 Section of lymphatic gland Transverse section of filarial worm with giant cells surrounding it

granulation tissue fibroblasts appear and eventually the remains of the worm are encapsulated and may become calcified This process may be associated clinically with a sharp **local inflammatory reaction,** and in some cases with a febrile attack Later there will always be scar formation which will further interfere with lymph flow in this region

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ction and stagnation

results Lymph ceases to drain from the tissues and the part becomes progressively more swollen Such tissue is known as **blubbery tissue** and when one cuts into it the lymph exudes and the tissue collapses

Drinker and his coworkers (1934 1935) have shown that this lymph has a higher content of plasma protein than ordinary lymph and that this content is further increased by any inflammatory reaction The high content of plasma protein increases the fibroblastic activity of the tissues

• In course of time the fibroblasts in the blubbery skin multiply and form new fibrous tissue which makes the skin dense and hard—the typical **elephantoid skin** The fibrous induration extends deep down into the lower layers of the skin as far as the sweat glands interfering with the lymphatics *in that region and producing œdema followed by* fibrosis around the sweat glands which are eventually destroyed so that the skin in elephantiasis is always harsh and dry In the meantime the surface hypertrophy of the epidermis becomes more and more marked fissures occur in the ill developed horny layer and allow micro organisms to invade the corium In these very large warty **elephantoid limbs** repeated attacks of inflammation originating at the surface and due to secondary bacterial infection are extremely common and increase the local hypertrophy

When the obstruction is in the deeper lymphatics the hypogastric and/or the common iliac the lymph is dammed back causing **lymph varices** of the abdominal plexuses and spermatic cord these may rupture into the peritoneum kidney bladder or tunica vaginalis causing **lymph ascites lymphuria lymphocele,** or if the obstruction is in the pre aortic nodes through which pass the lymph vessels from the small intestine and some of those from the pelvis of the kidney and which are also connected by small vessels with the lumbar lymph nodes this will lead to a reflux of chyle into these plexuses and if they rupture **chylous ascites chyluria,** and **chylocele** will result

The entrance of more and more mature filariæ into these dilated tortuous lymphatics keeps up the irritation of the vessel wall so that the endothelial cells hypertrophy and form — + e mass which projects into the lumen like a pap trauma is likely to rupture the blood vess and cause bleeding into the lymph vessel **hæmatocele,** etc

When the *back pressure extends to the lacteals these may dilate and* eventually rupture into the intestinal tract this reflux flow of chyle may cause **chylous diarrhœa,** but a much more serious sequel will be infection spread backwards serious septic com

As long as *the lymphatic obstruction is only partial or intermittent* **microfilariæ** will find their way into the blood stream but if it is complete the larvæ are confined behind the trophic limb and do not appear i that in cases of chyluria and lym almost always *found in the blood* are frequently not found (*vide supra*)

The importance of **secondary bacterial infection** is a controversial subject Some workers *including* Leiper (1924) Acton and Rao (1929) and Grace and Grace (1931) believe that staphylococcal or streptococcal infections play an imp processes of a hat most of the the skin can be the body of the part of the host worm itself ... (O Connor 1932) All recent work has supported the latter view and has *often shown the complete* absence of septic organisms in the early inflammatory lesions The allergic lesions may be some distance from *the actual*

worm, and the supporting tissues around the genital organs, e g the cord

ruptured

The variations in the lesions produced —Various explanations have been suggested for the differences in the lesions produced by filarial infections in different individuals, but the following explanation appears to the writer to have most support from his personal experience and from recorded data

If the complication of sepsis is excluded, there are two factors concerned, both of which are variable, namely (*a*) the tolerance of the subject to filarial metabolites, and (*b*) the intensity of the infection to which he or she is subjected

The human host will fall into one of the four following categories —

(i) *tolerant individuals subjected to few infected bites* their tissues

(ii) *tolerant individuals subjected to a heavy infection* in course of time mechanical blockage of the lymph nodes may occur causing some static œdema, lymph varix, or both without necessarily any lymphangitis or febrile reactions

(iii) *intolerant individuals subjected to few infected bites at long intervals* little damage is caused to the distal lymph nodes since they have time to recover between successive passages of the injected larvæ, all of

h nodes, *e g* the
which eventually
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occurs that the serious and often fatal acute funiculitis follows

(iv) *intolerant individuals subjected to many infected bites throughout the year* the distal lymph nodes
trochlear, are damaged early and o
come to maturity and parturiate in
periodic attacks of lymphangitis anc
completely blocked, with resultant elephantiasis, none or few microfilariæ can reach the peripheral blood

There is no reason to believe that tolerance is a fixed quality, and

If now, one of the possible common septic complications is added—such as infection from the skin surface in elephantiasis or from some hollow viscus into which a lymph or chyle varix has ruptured, or possibly

In course of time the fibroblasts in the blubbery skin multiply and form new fibrous tissue which makes the skin dense and hard—the typical **elephantoid skin** The fibrous induration extends deep down into the lower layers of the skin *as far as the sweat glands interfering with the lymphatics* in that region and producing œdema followed by fibrosis around the sweat glands which are eventually destroyed so that the skin in elephantiasis is always harsh and dry In the meantime *the surface hypertrophy of the* epidermis becomes more and more marked fissures occur in the ill developed horny
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When the obstruction is in the deeper lymphatics the hypogastric and/or
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through which pass the lymph vessels from the small intestine and some *of those from the pelvis of the kidney and which are also connected by* small vessels with the lumbar lymph nodes this will lead to a reflux of chyle into these plexuses and if they rupture **chylous ascites, chyluria** and **chylocele** will result

The entrance of more and more mature filariæ into these dilated tor tuous lymphatics keeps up the irritation of the vessel wall so that the *endothelial cells hypertrophy* and *f*
which projects into the lumen like a
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and cause bleeding into the lymph ves
hæmatocele, etc

When the back pressure extends to the lacteals these may dilate and eventually rupture into the intestinal tract this reflux flow of chyle may cause **chylous diarrhœa,** but a much more serious sequel will be infection of the dilated and damaged lacteals which infection may spread backwards to the larger lymph vessels *so that when they rupture serious septic com plications are likely to follow*

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The importance of **secondary bacterial infection** is a controversial sub ject Some workers including Leiper (1924) Acton and Rao (1929) and Grace and Grace (1931) believe that staphylococcal or streptococcal in fections play an important part in *all the inflammatory processes* of a filarial attack whereas others question this and believe that most of the milder inflammatory reactions except those originating in the skin can be attributed to *the irritation of the filarial secretions* and of the body of the worm itself and to an allergic response to these on the part of the host (O Connor 1932) d the latter view and has
often shown the rly inflam
matory lesions the actual

worm and the supporting tissues around the genital organs e g the cord and testicle appear to be particularly prone to allergic reaction The more serious complications however such as acute suppurating funiculitis peri tonitis and septicæmia are obviously due to secondary infection which may have been hæmatogenous in origin but is more likely to have resulted from direct infection from some hollow viscus into which the varices have ruptured

The variations in the lesions produced —Various explanations have been suggested for the differences in the lesions produced by filarial in fections in different individuals but the following explanation appears to the writer to have most support from his personal experience and from re corded data

If the complication of sepsis is excluded there are two factors con cerned both of which are variable namely (*a*) the tolerance of the subject to filarial metabolites and (*b*) the intensity of the infection to which he or she is subjected

The human host will fall into one of the four following categories —

(i) *tolerant individuals subjected to few infected bites* their tissues do not react to the filarial metabolites so that the migrations of the pre adult worm and parturition of the adult cause little or no reaction and no clinical symptoms but microfilariæ will always be found in the blood once the worms reach maturity

(ii) *tolerant individuals subjected to a heavy infection* in course of time mechanical blockage of the lymph nodes may occur causing some static œdema lymph varix or both without necessarily any lymphangitis or febrile reactions

(iii) *intolerant individuals subjected to few infected bites at long in tervals* little damage is caused to the distal lymph nodes since they have time to recover between successive passages of the injected larvæ all of which pass through these nodes to reach the deeper lymph nodes e g the

which eventually
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occurs that the serious and often fatal acute funiculitis follows

(iv) *intolerant individuals subjected to many infected bites through out the year* the distal lymph nodes e g the superficial inguinal and epi trochlear are damaged early and obstruct the passage of filariæ which come to maturity and parturiate in the lymph nodes of the limbs causing periodic attacks of lymphangitis and fever Soon the lymphatics become completely blocked with resultant elephantiasis none or few microfilariæ can reach the peripheral blood

There is no reason to believe that tolerance is a fixed quality and

If now one of the possible common septic complications is added—such as infection from the skin surface in elephantiasis or from some hol low viscus into which a lymph or chyle varix has ruptured or possibly

a hæmatogenous infection from some septic focus *e g* an apical absce or bowel focus—or if the rarer complications of hæmorrhage occurs it w be seen that a very large variety of clinical manifestations can be account for

Blood picture—There is no characteristic blood picture in filarias With the exception of an inconstant eosinophilia any of the changes th occur can be attributed to complications

The sternal puncture count done in a series of 53 cases of filarias showed about normal percentages for all the blood elements (Napier D Gupta and Rao 1941) the low percentage of eosinophil myelocytes cases in which there is an increase in blood eosinophils suggests an extr medullary origin for the latter

s in which there are micro
is of lymphatic obstructio
there is never any increa
a absent from the peripher
blood

Microfilariæ in the blood—Reference should be made to the para graphs on microfilarial periodicity and on the correlation between filaris infection and filarial disease above

We have found fewer microfilariæ in the sternal marrow than in th peripheral blood both during the day and during the night

Urine—There are no characteristic changes in the urine in an ordinar case of filariasis

In chyluria the urine is typically a milky white but the colour is no constant in a doubtful case the urine should be shaken up with ether o chloroform to see if it clears as it will do if the milkiness is due to fat If there is any doubt the urine should be examined again one to four hour after a fatty meal In chyluria as also in lymphuria the urine will coagu late on account of the presence of fibrinogen If it is set aside it wil separate into three strata an upper milky stratum a middle pinkish on in which the clot will be seen and a lower stratum consisting of cells an debris

Microfilariæ will be found in about fifty per cent of the cases either in the lowest layer or in the clot or one can demonstrate them by drop ping a few threads of cotton wool into the urine allowing these to sink to the bottom and then recovering a thread and examining it under the low power of the microscope

The fat content will vary from a trace to just over one per cent and the albumin from a trace to 0 6 per cent

In lymphuria there is albumin and many lymphocytes but except for the possible presence of clots the gross appearance of the urine is little changed

In hæmatochyluria and hæmatolymphuria there will in addition be red cells and some free hæmoglobin

SYMPTOMATOLOGY

Classification—From the description of the pathological proces es given above it will be obvious that the clinical pictures produced may be quite varied As has been indicated above there may be a short lived skin

lesion—redness and induration with some irritation—at the point of entry of the larvæ, but this is inconstant and is seldom remembered by the patient, it therefore need not be considered in the symptomatology Otherwise the following classification covers the commonest of the filarial syndromes

A Signs and symptoms may be absent

B Lymphangitis and lymphadenitis
 (i) Uncomplicated
 (ii) Septic which may subside or lead to
 (iii) Abscess formation

C Elephantiasis
 (i) Uncomplicated
 (ii) Complicated by sepsis
 Either may involve
 a) The limbs
 b) The scrotum penis or labia
 c) The mammæ

D Lymph varix superficial or deep
 (i) Uncomplicated
 (ii) Rupturing and producing a variety of non septic complications
 a) Lymphorrhœa of the groin or scrotum
 b) Filarial synovitis
 c) Lymphocele (hydrocele)
 d) Lymphuria
 e) Lymph ascites
 (iii) Bleeding as a result of trauma and producing
 a) Hæmatospermia
 b) Hæmatocele
 c) Hæmaturia or hæmatolymphuria
 (iv) Suppurating before or after rupture

E Chyle varix
 (i) Uncomplicated
 (ii) Rupturing and producing a variety of non septic complications
 a) Chylocele
 b) Chyluria
 c) Chylous ascites
 d) Chylous diarrhœa
 (iii) Bleeding may occur as in lymph varix and produce a parallel series of complications
 (iv) Suppurating before or after rupture

F General symptoms
 (i) Fever
 (ii) Allergic manifestations
 a) Skin manifestations e g urticaria
 b) Extra focal inflammatory swellings especially of the genitals
 c) Asthma

G Psychoneurotic manifestations

A full clinical description of each of the very numerous filarial manifestations classified above would be out of place here but notes are given below on the commoner ones and on those that seem to require some explanation As far as they are applicable the paragraph identifications used above are followed

Incubation period—It is usually stated that microfilariæ first appear

can be obtained from the age at which persons born in an endemic area first show symptoms In many filarious countries, it is seldom that evidence of lymphatic obstructions appear within fifteen years of the date or ar-

rival in an endemic area although in such cases there will often be a history of periodic febrile attacks with possibly some lymphangitis for several years However in highly endemic areas this period is frequently much shorter and recently from the South Pacific cases have been reported in which the incubation period was apparently only three and a half months lymphangitis of the arm and of the spermatic cord was associated with fever and the finding of the adult worms but not of microfilariæ

A **Symptomless* infection** —In most endemic areas the majority of the infections are symptomless and in the areas of low and moderate endemicity they remain so indefinitely However as fresh infections are super imposed on account either of sheer weight of numbers of adult worms or of developing intolerance on the part of the host some of these subjects will later develop symptoms and naturally the numbers of such persons will vary in direct proportion to the intensity of the infection to which they are subjected (*vide supra*)

B **Lymphangitis and lymphadenitis** —(i) ***Uncomplicated*** —Attacks may occur at frequent and often regular intervals it is commonly noted by patients that the attacks recur always at some particular phase of the moon or in women at one particular state of the menstrual cycle The whole limb and the glands in particular are very painful and often a red

of cases The site of the adult worm may be indicated by a particularly red and tender spot

The local symptoms are usually accompanied by a febrile attack temperature 100° F to 102° F with general malaise headaches and pains all over the body that usually lasts for two or three days The local symptoms may subside after four or five days

Not infrequently the general symptoms appear without any definite localizing symptoms and conversely *local signs may be unaccompanied by fever*

(ii) If ***sepsis***, either hæmatogenous or otherwise, is added the local and general symptoms will be of a more severe nature the whole limb being very swollen and red and the temperature running up to 104° F or 106° F daily for a week or more When such an attack subsides the limb seldom returns to its previous diameter

(iii) A local ***abscess*** at the site of the dead worm may be left (figure 169)

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occurs

The bizarre deformities that filarial infection will produce are we
known they are capitalized in the East by beggars who parade them f
the purpose of obtaining alms and in the West by writers of textbool
who always seek the most extreme examples for decorating their page



Figure 169 Scars of *filarial abscesses* left arm along main lymphatic vessel

D **Lymph varix**—Varices will occur mainly when the vessels l
superficially or in loose cellular tissue and are therefore relatively unsu
ported Lymph varix may thus be found on the surface of a limb or
the groin (figure 175) in the spermatic cord in the scrotum or in the dee
abdominal lymphatics in the bladder wall or around the kidney

They may be (i) uncomplicated or (ii) the varix may rupture (*a*)
the surface in the groin or scrotum producing lymphorrhœa (*b*) into
joint *e g* knee or hip causing filarial synovitis (*c*) into the tunica causi
a lymphocele (hydrocele) (*d*) into the urinary bladder or the kidn
pelvis or calices causing lymphuria or (*e*) into the peritoneum causi
ascites A characteristic of lymph varices is their sudden disappearan

and reappearance within a few days Otherwise these conditions are mostly self explanatory, two only appear to need further description

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ation is under
tal i the part tha
may amount to seven or eight ounces o and this keep
the patient s clothes continuously wet

(d) The onset of **lymphuria** is often insidious but is at other time
h an aching pain in the bladder or the loin or in botl
n the urine and man
gross appea



Figure 174 Elephantiasis of the vul a

f The complications caused by the hæmorrhage into the
t mainly on trauma are lik
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The most serious of the septic complications is acute fun
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matogenous in
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ute abdominal
gency It may occur in a patie h varix or lym
for some time or it may appear as an early even if not the first syr
complications are even more likely to occur in cases c
may be the in

E *Chyle varix*

(i) Chyle varix is probably less frequently **uncomplicated** and symptomless than is the corresponding lymph condition, but it also may be un complicated The condition will usually cause a certain amount of abdominal discomfort backache, or pain in the loin

(ii) and (iii) (a) **Chylocele** is also less common than lymphocele but does frequently occur *The swelling will not transmit light and is very likely* to be complicated by a certain amount of hæmorrhage (**hæmatochylocele**) it might, therefore be mistaken for a strangulated hernia if not carefully *examined*



Figure 175 Lymph varix of cord (bilateral) and lymph scrotum

(*b*) **Chyluria,** on the other hand is more common than lymphuria Attention is usually drawn to the condition by the patient s noticing that his or her urine is milky but it may be preceded by back pain and aching in the pelvis and loin in women the onset of chyluria or **hæmatochyluria** may follow childbirth and in men any form of physical strain A very troublesome complication is urinary retention due to the presence of clots in the bladder that periodically block the urethra In the case of kidney chyluria the clots may block the ureters temporarily it is seldom that there is clinical evidence of this but occasionally there will be typical renal colic

An excretion pyelogram will often show more dilatation of the ureters and during cystoscopy, it is not uncommon to see the clot being slowly extruded from the ureteric orifice In about three quarters of the cases the dilated lymph vessels can be seen usually just above the ureteric bar but sometimes lower in the trigone

The chyluric attack usually lasts about a week or ten days and then clears up entirely for some months but sometimes it will last for several

(*c*) **Chylous ascites** *will not be distinguished clinically from ordinary* filarial ascites due to the rupture of a lymph varix, but will be apparent when paracentesis is performed septic complications are more likely to occur than in the simple ascites and in this case the picture will be one of peritonitis

(*d*) **Chylous diarrhœa** resulting from the reflux of chyle into the intestinal canal has been reported but is apparently a rare filarial manifestation

(*iv*) **Suppurating** It will not be necessary to discuss the septic complications that may be associated with any one of these ruptures of chyle varices but in view of the closer association with the intestinal canal they are likely to be commoner than in the case of lymph varices as has been indicated above

F **General Symptoms**

(*i*) **Fever**—The fever that develops in filariasis is due either (*a*) to the worm and/or its metabolites entirely independently of secondary infection and for this the accepted expression filarial fever is quite appropriate or (*b*) to secondary infection of the blocked lymphatic channels of the elephantoid skin or of the varices and for this the expression secondary fever to which the words of filariasis might be added if the context did not already make it clear seems to be unobjectionable *

(*ii*) **Allergic manifestations**—There is undoubtedly a form of urticaria that is associated with a filarial attack and often recurs at regular inter

festations The writer can give no statistical data in support of this clinical impression

G **Psychoneurotic manifestations**—The psychoneurotic effects were apparent in young white and Anglo Indian girls who living in the poorest parts of certain Indian towns—Calcutta for example—in close association with the native population frequently became infected with filaria but

genital location of the lesions (*b*) occasional associated venereal disease (*c*) the frequent deformities in the natives with whom they associated (*d*) the alarming pictures in medical textbooks to whose influence they were too often directly and indirectly subjected and (*e*) the ill advised publicity given to the whole incident led to the development of psychoneurosis in a very large percentage of those with even the mildest somatic lesions It has been estimated that 90 per cent of the disability of the personnel invalided on account of the infection were of psychoneurotic origin

* The fever that occurs when elephantoid skin and tissue become infected has been called elephantoid fever Not only is the expression elephantoid fever an example of a ridiculously misapplied adjective but it is misleading as the fever that develops when secondary infection occurs in other filarial conditions such as lymph or chyle varices has exactly the same ætiology and the expression elephantoid fever applied in these cases would be even more ridiculous

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

This must be considered under a number of headings —

(a) **Duration of residence in an endemic area.**—The time taken for

(b) **History of a previous attack.**—A history of previous attacks of lymphangitis without any apparent local cause, followed by œdema of the limb that does not always subside, and associated with a mild or severe febrile attack, should arouse great suspicion Periodic febrile attacks alone in cases in which malaria can be excluded are also suggestive

(c) **Clinical picture**—The acute painful descending lymphangitis and lymphadenitis with fever should always be viewed with suspicion in an endemic area, but they may have other causes, the lymph varix, brawny œdema and elephantiasis of the limbs, genitalia, or breasts will be more characteristic, but are only evidence of lymphatic obstruction—the most common cause of which in the endemic areas is, of course, filariasis—and not *per se* of filariasis itself, and certain other lesions that commonly occur in filariasis, such as hydrocele, are as likely to have some other cause even in endemic areas

When hypertrophy occurs in other regions where there is a good col

(d) **Laboratory examinations**—(i) *Blood*—The examination of the blood for microfilariæ has its strict limitations as a means of diagnosing filarial disease, see p 664, correlation between filarial infection and filarial disease

f micro

ire

In countries where the infection is transmitted by *Culex fatigans* or

and the microfilariæ show nocturnal perio-

o'clock at night

ch as Fiji where

ken at about *10*

Technique—Take about 20 c mm of blood preferably an accurately measured

from the finger or ear and make a thick

to dry *then stain and dehæmoglobinize*

stain very carefully—do not wash it off

Dry the film in air and

low power lens The number of microfilariæ will vary from one in many films to hundreds in one film by multiplying the number per thick smear by 50 the number per c cm will be arrived at

threads

The microfilaria of *W. bancrofti* has a sheath. Figure 176 may help in the differentiation of this microfilaria from those of other filarial worms.

No assistance will be obtained from the blood count. Eosinophilia, though frequently present, is too inconstant a finding to be of either positive or negative value.

(ii) ***Immunological tests.***—A complement fixation test in which the antigen is prepared from the dog filaria *Dirofilaria immitis* has proved successful but apparently is dependent on the worm being alive.

The simpler intradermal test has been used more widely, but there is considerable variation in the technique used. A 1 in 8000 *Dirofilaria* antigen with 0.3 per cent phenol, of which 0.01 c.cm. is given by means of a tuberculin syringe, gives a minimum of false positive reactions even in allergic individuals. A weal of at least 1 c.cm. in diameter will indicate a positive reaction. A. H. Hamilton (personal communication), basing his opinion on experience in the East Indies, considers that positive intradermal tests with dirofilaria antigen are of little value since about two out of three normal natives will show positive results. A negative test, however, he considers to be of the greatest value as excluding filarial infection.

These intradermal tests, for which a really satisfactory standard technique has still to be found, indicate rather the reactivity of the host than the presence of the worms. Their particular usefulness will not be in a highly endemic area, but to diagnose an obscure lymphangitis in a patient who has at one time been in an endemic area but shows no microfilariæ in the blood.

A flocculation test with hydrocele fluid has a limited usefulness.

(iii) **Urine.**—The milky urine in chyluria can be identified with the naked eye. For the method of examination for filaria *see* p. 672.

(e) **Other procedures.**—These include cystoscopy and pyelography to identify the sites of the ruptured lymph varices in chyluria, roentgenography to show the presence of calcified filariæ, and gland biopsy to identify the adult worm.

PREVENTION

This must be considered under two headings—

A. The prevention of the spread of infection; and
B. The prevention of attacks in those already infected.

A. **Prevention of the spread of infection.**—The reader should refer back to p. 666, where the essentials for transmission and the factors concerned in endemicity are discussed. These are:—

(i) The source of infection: microfilariæ in the peripheral blood of man.
(ii) The vector mosquito.
(iii) Susceptible man.
(iv) The links between (i) and (ii), and (ii) and (iii).

This aspect of prevention can be discussed shortly under each of these four headings

(i) Man is the only source of microfilariæ, but in highly endemic areas a very large percentage of the community will have them in their blood Further, there is no drug that has more than a very temporary effect on the microfilariæ in the blood Therefore, any attempt at wholesale 'sterilization' of infected individuals is at present out of the question

Segregation of infected communities should as far as possible be practised *This may be advisable when labour forces, police, or armies are recruited from endemic areas, and are to be employed in areas where transmission is possible*

Again, the circumstances might be such that it would be advisable to weed out altogether those who had microfilariæ in their blood If this were decided upon, it would be advisable to examine several night blood specimens from each individual

In endemic areas, the highest infection rate is amongst the poorer classes of people who have made no attempt to protect themselves from mosquito bites, so that the uninfected should build their houses well away from poor-class dwellings and should see that any servants that are allowed to sleep in their houses are free from blood microfilariæ

(ii) Control of the transmitting mosquito will provide the most promising line of attack While at least a dozen species belonging to four genera, *Culex*, *Aedes*, *Tæniorhyncus*, and *Anopheles*, have been found infected in nature and many others have been infected experimentally, *Culex fatigans* is the predominant transmitter in India and in many *other tropical countries* It is a night-feeder, a breeder in dirty and stagnant water, and comparatively local in its habits, it is therefore not very difficult to control around dwellings by the usual measures directed against either larvæ or ... main trans-

... hat species

..., but some

... pages 113 to 117

(iii) There is nothing to be said under this heading as there is little evidence that there is any individual immunity to *infection*, and there is certainly *no evidence that it is possible to induce or increase such immunity*

(iv) In institutions, or even in households, infected persons must be kept in mosquito-proof rooms, or at least under mosquito nets at night, in order to prevent infection of the local mosquitoes

Conversely, for personal protection in mosquito-ridden endemic areas, *screening, mosquito nets, repellents, etc, should always be used, as a pre*caution against being bitten by infected mosquitoes

B **The prevention of attacks in those already infected**—The most

tract, or a bowel lesion, such as ...
Elimination of such a focus, *e g*
course of carbarsone or diodoquin,
of febrile attacks that a patient suffers

This precaution should be taken in all infected persons whether they have suffered previous attacks or not

However as well as by removing septic foci persons who have already had attacks of filarial lymphangitis or some other filarial syndrome can reduce considerably the chances of further attacks by maintaining good general health and if possible moving to a cooler climate A recommendation to this effect usually can be made with a clear conscience as even if such persons have microfilariæ in their blood and there are *Culex fatigans* or other vectors in the locality they will not be a source of danger to the new community amongst whom they go to live provided the temperature and humidity are outside the ranges within which transmission occurs (*vide supra*) It is however quite unnecessary to recommend such a measure as transfer to a cold climate for an infected person who has suffered no clinical attacks except of course as a means of preventing further infection

TREATMENT

Introduction—The treatment of this condition is more unsatisfactory than that of almost any other tropical disease but partly because of this and also because of the variety of the clinical conditions that occur in filarial infection a very great deal has been written on it It is proposed to treat the subject summarily here It can best be considered under the following headings —

A Specific treatment

B Treatment of secondary infections

C The relief of lymphatic obstruction

D Palliative treatment for special conditions

A **Specific treatment**—No true specific has yet been found but there does not seem to be any valid reason why at some future date one should not be expected Some drugs when given intravenously appear to destroy the microfilariæ but this does nothing towards helping the patient for the adult worm which is not in the blood stream is left intact When the adult worm has once settled in the tissues it is difficult to reach it The best [illegible]

[illegible] the treatment to the heavily infected

Antimonyl tartrates were used by Rogers in 1917 but it was shown [illegible]

out success Systematic clinical experiments with various drugs have been carried out by Rao at the Calcutta School of Tropical Medicine during the last twenty years Patients at various stages of the infection were treated by drugs whose therapeutic efficiency in other parasitic infection was known The results may be briefly stated —

Of the organo metallic compounds, soamin (atoxyl) appears to be most satisfactory in controlling the *symptoms in the early stages* It can be given subcutaneously, intramuscularly, or intravenously, and is usually non-toxic, although a few exceptionally susceptible persons, who exhibit toxic symptoms even after the first injection have been encountered There does not appear to be any appreciable reduction in *microfilaria count even* after a full course of treatment with this drug, but in many cases the patients have remained free from fever and lymphangitis for a long time after treatment with soamin Certain other arsenic compounds such as tryparsamide novarsenobillon and sulfarsenol, have given almost as satisfactory results as soamin, tryparsamide, given in 2 to 3 gramme doses, intravenously, appeared to control the symptoms in chyluria in particular

Practically all available organic compounds containing antimony were investigated *Of* these the pentavalent neostibosan* and the trivalent compound Fouadin gave the most satisfactory results The latter drug can be administered subcutaneously, intramuscularly or intravenously and is non toxic The effect of these drugs on the filarial parasites seems to be temporary as the *microfilariæ reappear in the blood after the lapse of some* days though it may be several weeks before they reach their previous level These drugs usually control the inflammation and fever for a considerable time

' ' drugs used in this disease is anthio Some workers have claimed good ints, f r several months at least It is given intramuscularly in doses of 2 c cm to 4 c cm of a 6 per cent solution according to the patient's tolerance, on alternate days up to 10 doses

Several vegetable drugs which are reported to be efficacious in allied helminthic infections were administered orally and in some cases by injection Oil of chenopodium appeared to give satisfactory results in some cases when given intramuscularly, it reduced the number of embryos in the circulation and controlled the attacks of lymphangitis but the injections caused painful reactions

B **Treatment of secondary infections**—This should be considered under the headings —

(i) Local treatment
(ii) General chemotherapeutic treatment
(iii) Vaccine treatment
(iv) The search for and eradication of septic foci

(i) ***Local treatment*** will naturally depend largely on the part affected and the nature of the lesions Ulcers on an elephantoid leg will in some cases be benefited by elevation of the limb followed by the application of powdered sulphonamide to the ulcerated area and tight strapping of the whole affected part of the limb with elastoplast or some similar material which must be left for several days

For lymphangitis and lymphadenitis whether there is secondary infection or not hot fomentations and local application of heat by the infra red lamp will relieve the pain and reduce the inflammation

* Recent work by Culbertson and Rose (1945) suggests that neostibosan given in much larger doses than hitherto employed progressively reduces the microfilaria count—to nil in some instances—and that the reduction persists for at least 8 months —the length of duration of observation

(ii) Of the *general chemotherapeutic* agents the new 'sulpha' drugs have proved very useful in the treatment of secondary infections of all kinds and very satisfactory results have been obtained in the treatment of such very serious conditions as epididymo orchitis and funiculitis by the administration of red prontosil, sulphapyridine and sulphathiazole have also proved very effective, but it is probable that new and more effective anti streptococcal drugs *e g*, penicillin will be in general use by the time this chapter is printed

(iii) *Vaccines* have been the mainstay in the treatment of many filarial lesions for some time and it seems doubtful if the good effects claimed and in some cases undoubtedly produced can be attributed to the specific

ection The effect has probably
in many cases This has ob-
workers who have used typhoid

A vaccine, consisting of 10 million hæmolytic streptococci of many strains and 50 million staphylococci of several strains of *aureus* and *albus* has been used by Rao at the Calcutta School of Tropical Medicine over a period of 15 years in more than 50,000 cases The vaccine is given intracutaneously in doses of 0 02 to 0 1 c cm twice weekly up to a total of 15 to 20 injections The ameliorative effects have been sufficiently encouraging for him to consider that, in the absence of a specific this is the best treatment to give, even when there is no evidence of secondary infection Other workers have used autogenous vaccines and claim satisfactory results

(iv) The **septic focus** that gives rise to the hæmatogenous infections should be sought and removed (*see* p 670)

C **The relief of lymphatic obstruction** —Attendance to the general health of the patient is important and very often if the patient is sent away to a place with a more bracing climate there will be some reduction in the size of the limb and therefore presumably an improvement in lymphatic drainage

During an attack of lymphangitis the obstruction is temporarily increased by the inflammation and œdema and the speed with which the permanent fibrotic obstruction develops will depend to a large extent on how long this is allowed to persist so that rapid relief is important This is helped by rest, elevation of the limb and, if it is not too tender firm bandaging with an elastic bandage Vaccine and non specific protein treatment are also useful in this capacity

For relief in the quiescent stage, surgeons have devised innumerable operations for the re establishment of lymphatic drainage with little evidence of success Better results are obtained even at this stage by bandaging the limb tightly Several forms of permanent bandage have been devised some are made of elastic webbing and others of more rigid material such as muslin or even canvas but fitted with zip fasteners at the top and bottom so that the pressure can be regulated and released when necessary By this means support is given to the distal lymph vessels and drainage through collateral lymph channels is encouraged, massage and exercise aid this

D **Palliative measures** —Very often the first demand on the attending physician will be for the treatment of the **acute lymphangitic attack** and this subject has not been specifically covered above Rest, elevation of the

limb, hot fomentations, infra-red rays or even short-wave diathermy ap

such as lead or calamine

with aspirin and phenace-

justifiable to give morphia,

but it should seldom be necessary to repeat this A brisk saline purgative, a light diet, rest and the continuance of the local treatment, and perhaps a sleeping draught for the next few nights will be sufficient to help the patient through an uncomplicated attack, but, if there is any evidence or even any suggestion of there being secondary infection, it will be as well to give sulphonamides and possibly the other treatment recommended for secondary infection (*vide supra*)

In certain cases, in order to relieve the pressure—and therefore the pain—during an acute attack, small skin incisions have been made with a very sharp knife and a local anæsthetic under aseptic conditions, through these, lymph drains and relieves the tension, but the procedure is not to be recommended as permanent sinuses may remain and these are not only troublesome to the patient but may later become infected

The inconvenience and discomfort of **massive elephantiasis** of a limb will sometimes be relieved by Auchincloss' operation, or some modification of it In this operation, two parallel skin incisions joined at each end by a V-shaped incision are made in the long diameter of the limb, a wedge shaped piece of skin and blubbery tissue is removed the skin under cut on each side and then drawn together, and the wound closed If possible

Large scrotal swellings have frequently been removed very success fully, but the operation is not without hazard and should be preceded by a blood transfusion As these swellings may reach a weight of one, or even two hundred pounds, their removal is a very great relief to the patient This also applies to elephantiasis of the mamma and vulva, but, if opera tion is undertaken, nothing short of complete removal should be attempted

Chyluria should be treated by complete rest, the elimination of all fat from the diet, and saline aperients If there are clots in the bladder, this may have to be washed out with warm boric lotion of 2 per cent sodium

also recom

cystoscopy

ration has

PROGNOSIS

Filariasis is not a fatal infection and the expectation of life of the filarial subject is not materially decreased There are a few of the rarer complications of obstruction of the deep lymphatics such as acute sup- purating funiculitis which usually leads to peritonitis, that are very fatal, but they occur in a very small percentage of the persons attacked Again, in cases of extensive elephantiasis, ulceration and sepsis may cause exhaus- tion and eventually death

Many filarial subjects attain a considerable age, and it has even been suggested that the enforced inactivity which the disease may entail actually tends to lengthen the expectation of life

There is every indication that the serious deformities that are associated with this infection only develop in persons subjected to repeated infection continuously over a number of years, so that even those with heavy initial infections will be very unlikely to develop serious sequelæ if they are removed from the source of infection

There is no indication that filarial lesions of the genitalia lead to impotence or sterility as, even when there are considerable deformities, vital tissues are not involved

FILARIASIS DUE TO WUCHERERIA MALAYI

Historical—The embryo of *Wuchereria malayi* was described by Brug (1927) from Java and named *Microfilaria malayi*, and the adults were first seen and described by Rao and Maplestone (1940) in a biopsy specimen taken from a patient in North Travancore

Geographical distribution—This is a parasite of rural areas with a patchy distribution *Wuchereria malayi* is the chief filarial parasite in Malaya It is common in Sumatra, Java, Borneo, Celebes New Guinea, Indo-China, South China, India, and Ceylon In India, it is found in a few places in North Travancore, Orissa, the Central Provinces, Santal Parganas, East Bengal, and Cachar (Assam)

ÆTIOLOGY

there are two pairs of smaller papillæ There are two spicules which are unequal and dissimilar, and a small boat-shaped gubernaculum

The female worm measures 55 mm in length with a diameter of 0 16 mm The mouth is terminal without appendages or lips The vulval opening is 0 98 mm from the tip of the tail The general course of the uterus and its branches ending in ovaries is practically the same as in the female of *Wuchereria bancrofti*

The ovum varies greatly in size, measuring 0 027 mm long and 0 018 mm broad

The average length of the microfilaria in the fresh state is 263 microns, while in smear preparations it is 186 microns (177 230 microns) The most distinctive character in the microfilaria of this species is the presence of two discrete nuclei at the tip of the tail (*see* figure 176)

The adult *Wuchereria malayi* lives in the lymphatics of the extremities in man and the sheathed embryos circulate in the blood showing a nocturnal periodicity

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1935
grass' (Fraser, 1938) and in Malaya in mangrove swamps

SYMPTOMATOLOGY

The pathological lesions produced by this parasite consist mainly of lymphatic obstruction of the extremities There seems little support for the oft repeated statement that the lesions are usually in the upper extremities in *W malayi* infection (Rao 1936) Periodical inflammatory attacks

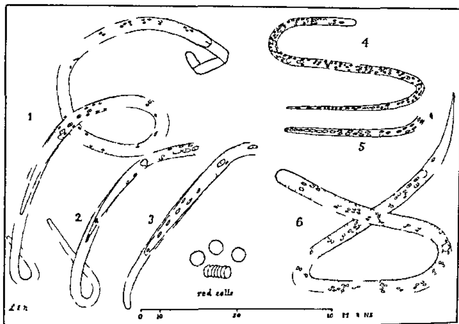


Figure 176 Showing the microfilariæ of

Sheathed	Unsheathed
1 *Wuchereria bancrofti*	4 *Mansonella ozzardi*
2 *W malayi*	5 *Acanthocheilonema perstans*
3 *Loa loa*	6 *Onchocerca volvulus*

of the lymphatic vessels and glands occasionally ending in abscesses are common No case of genital affection of hydrocele or of chyluria due to this parasite has so far been reported

PREVENTION

tion of bites
by in (1937) have
repor *alayi* infec
tion l ponds but
as in other plants
(Fraser *loc cit*) this method may prove disappointing

TREATMENT

m f h and chronic stages

FILARIASIS DUE TO LOA LOA INFECTION

Definition—Loaiasis or *Loa loa* infection is caused by the filarioid
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Geographical distribution—*It has a wide distribution in West and* Central Africa particularly along the River Congo and its tributaries A parasite of the same genus was reported by Maplestone (1938) from India, he gave it the name *Loa inquarenda* provisionally

Parasites—The average length of the male is 30 to 34 mm and the breadth about 0 4 mm *The cuticle is embossed with protuberances* The
The
d has

The microfilariæ exhibit diurnal periodicity and are transmitted by *Chrysops dimidiata* and *Chrysops silacea*

The infective third stage larvæ appear at the proboscis of these flies in about ten days but their growth to the adult stage in man is believed to take several years and they may live fifteen years

The baboon also acts as a host to this infection

SYMPTOMATOLOGY

*Generally the worm infection does not give rise to any signs or symp*toms However in some cases fugitive swellings as large as a hen s egg known as Calabar swellings occur on the course of the worm s migrations *The* worms migrate in the arms across the bridge of the nose across the eyeball under the *conjunctiva or in any other part of the body* The swellings are hot tender and painful they last for a few days or weeks and then disappear suddenly and they are probably allergic in nature

Other signs and symptoms of disease produced by this parasite are urticaria hydrocele lymphatic œdema and abscess

DIAGNOSIS

d the occasional passage of
rm can sometimes
nose and removed
for identification Puncturing or splitting the skin around the swellings will often reveal the microfilariæ but these are also found in the peripheral blood The specimen should be taken about midday Group intradermal and immunological reactions are also positive in this infection

PREVENTION

This consists in personal protection from the bites of tabanid flies and measures to control these flies

TREATMENT

No drug so far used has any lethal effect on the parasite in the human system *Cold applications of sedative lotions and compresses relieve the*

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DRACONTIASIS, OR GUINEA-WORM DISEASE*

* By the author and Dr S Sundara Rao filariasis research worker Calcutta School of Tropical Medicine

Definition.—Dracontiasis, or guinea-worm disease, is caused by the presence of large nematode worms, *Dracunculus medinensis*, in the tissues, it is characterized by a prodomal systemic reaction, local irritation at the site of the worm, septic complications at the point of its emergence, and local fibrotic sequelæ The disease occurs endemically in certain relatively dry regions in the tropics and subtropics, is very local in its distribution, and is associated with a specific set of conditions regarding water supply

Historical.—Guinea-worm infection is one of the oldest of tropical diseases The expression 'fiery serpent' in ancient Hebrew literature probably refers to this disease It seems possible that Moses knew the method of twisting the worm [illegible]

[illegible]

Our present knowledge about the spread of this infection dates from 1869 when Fedschenko a Russian biologist in Turkestan, showed that the embryo of [illegible]

[illegible] other workers, including Manson who in 1893 repeated the experiments in London and found that the ecdysis of the guinea-worm embryo in the local cyclopidæ took place in the sixth week Leiper, working in Africa in 1907, added further confirmation and produced the disease experimentally in monkeys

In 1913, Liston Turkhud and Bhave extended this work further and demonstrated at the Haffkine Institute, Bombay, that a man who drank water containing infected cyclops developed the worm in 348 days

Geographical distribution.—Guinea-worm disease is widely distributed in the tropics It occurs in Asia, Africa, and South America

[illegible] of the [illegible] n some [illegible] 's Do [illegible] areas) [illegible] North- [illegible] n parts of the Punjab

The disease does not occur at all in the north-east part of India, namely, in Bengal, Assam, and the adjoining provinces, nor in Ceylon, Malaya, or the East Indies (except possibly in some localities in the Dutch East Indies), Australasia, China, or the Pacific Islands Nor has it been reported from Europe or North America

ÆTIOLOGY

Morphology of the parasite.—A fully-grown female worm is 32 cm to 120 cm (12 to 48 inches) long and 1 5 to 1 7 mm (about 1/16th inch) in

diameter The worm is round, smooth and milky white in colour The head end is tapering and rounded The tail, also tapering, is curved like a hook The mature worm is packed with embryos from head to tail, there are about three million embryos in each worm

The male worm apparently measures from 12 to 40 mm long and 0 4 mm broad, but few specimens have been seen and these have mostly come from experimentally infected animals

Embryos are 0 5 to 0 75 mm long (1/42 inch) They have a flattened body and a tapering tail They lie coiled up on discharge from the worm but they soon stretch out in water and begin to swim vigorously with a tadpole like motion They can live in clean water for a week and much longer in muddy water There is no further development of the embryos until they enter the cyclops

Life Cycle —While in water, the embryos (first-stage larvæ) are swallowed by the cyclops (as many as ten may be seen in one cyclops), and migrate to the body cavity where they undergo further development, at the end of the fifth day the embryos lose their tapering tails they moult on the 9th day, develop a bilobed tail, and grow much longer All these changes take about two weeks in the summer months There is no further growth inside the cyclops

When infected cyclops are swallowed by man in drinking water, they are killed by the gastric juice in the stomach The larvæ which were sluggish hitherto become very active and escape from the dead cyclops, they pierce the intestinal wall and reach the loose retroperitoneal tissue where they develop further, and then migrate to other parts of the body of their definitive host The full development to the mature adult stage takes between eight months and one year

When the female becomes gravid, it migrates to the surface of the body, usually to those parts that are most likely to come in contact with water *e g* legs and feet When the worm reaches the site of choice it secret[illegible] amongst other things causes a local [illegible] Eventually, when it comes in con- [illegible]d the uterus prolapses through the [illegible]y-wall of the worm appears at the mouth of the opening, bursts, and discharges a milky fluid swarming with larvæ These pass into the water where they may live free up to about a week, after which they die, unless meanwhile they are swallowed by the cyclops present in the water, when the whole cycle may be repeated

The discharge of larvæ is determined by temperature, in nature by contact with cold water, but it can be precipitated by the application of a piece of ice, or an ethyl-chloride spray The migration of the adult worm may also be determined by thermotaxis, as in Rajputana, where *bhisties* (water-carriers) carry water in leather bags on their backs, and worms often appear on the back In the people who carry water in pots on their shoulders or head, the worm may appear on the neck, or even on the head itself

Whilst there is no evidence that man ever enjoys complete immunity from invasion by this worm, there is evidence from human experiments in Bombay, in which volunteers were fed large numbers of infected cyclops and only one developed a single worm infection, and from numerous animal experiments, that only a small percentage of the larvæ ingested by man reach maturity

Intermediate host (cyclops).—Cyclopidæ are present in many collections of fresh water and are found throughout the year They breed actively in the summer, they are fairly abundant in the rainy season (July through September), and they decrease slightly in the winter months They have a pear-shaped symmetrical body with a forked tail, two pairs of antennæ, five pairs of swimming legs, and one eye They measure about a twelfth of an inch and are just visible to the naked eye There are about six species of cyclopidæ in India They are

Mesocyclops leuckarti,	*Mesocyclops varicans,*
Mesocyclops hyalinus,	*Paracyclops fimbriatus,* and
Mesocyclops decipiens,	*Microcyclops karvei*

Other species of Cyclopidæ in which development may take place include *coronatus, magnus, prasinus, serrulatus, quadricornis, strenuus, vernalis, viridis,* and *vermifer* All of these feed readily upon the guinea-worm larvæ

Cyclops thus infected do not live as long as uninfected ones, but they have been found to live up to two months The average life of cyclops is about three months, but this period is considerably affected by the temperature of the water, and its acidity or alkalinity, they die when the water is warmed to a temperature of 60°C

EPIDEMIOLOGY AND FACTORS IN TRANSMISSION

It will be seen from the above description of the transmission cycle [illegible] on of the water [illegible] ence of suitable [illegible] (iii) consump- [illegible] nfected cyclops [illegible] mic are, therefore —

(a) a very special set of social and sanitary circumstances in which man, firstly, steps barefooted into the water when taking water for drinking or other purposes (theoretically man might contaminate the water by the immersion of other parts, and other animals might act as definitive host) and, secondly, drinks the water from this source without filtration or boiling,

(b) a water source in which cyclops will live and multiply,

(c) the actual presence of cyclops of certain species in sufficient numbers in this water, and

(d) the commencement of the cycle by the introduction of an infected person into the community

We will consider each of these conditions in association with known facts regarding the epidemiology of the disease

(a) **Special social and sanitary circumstances**—Dracontiasis is known to be limited in its distribution to towns and villages where such conditions exist

The water supply of a large number of villages in tropical and subtropical countries is from *tanks* (*i e* reservoirs) or step-wells At several points around the *tank* are stone, brick or concrete steps that extend into the tank two or three feet below the water level It is the local practice to walk down these steps into the water in order to fill the water-pot con-

veniently, even if the tank is reserved for drinking water, which i
always the case In fact, in many instances the villager will first

tank (Figure 177)

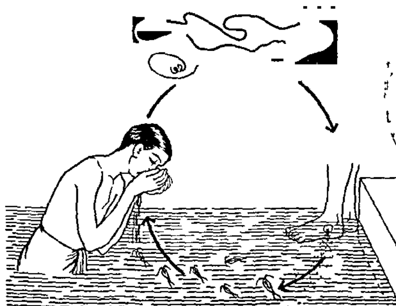


Figure 177 Indicates the transmission cycle in guinea worm disease

The type of water supply in use is often not a matter of free c
for the community, but is determined by soil and climatic condition
example, in very dry countries all natural water-supply must of nece
be from *deep* wells and the disease does not occur

Finally, educated individuals who have taken the precaution of b
or filtering their drinking water from these sources have avoided the di

(*b*) **Suitable water supply.**—Cyclopidæ are bottom feeders an
not flourish in deep wells, they require a certain amount of organic m
for their food, they are susceptible to chemical and physical changes i
water, they fall an easy prey to fish of many species, and finally,
naturally die out when a well dries up

The disease is confined to areas of moderate rainfall Rao has s
that the ... between 10 and 40 ...

12 inches, there are many heavily infected areas, and the disease never

nportant part in destroying

Further, the **incidence year by year** is dependent on the regular recurrence of suitable seasonal conditions, and deviations from these conditions have often been shown to affect the incidence Instances have been recorded where the disease has disappeared for several years after a flooding, which has washed out the cyclops from the wells, reduced the organic matter, and changed the chemical and physical composition of the water, and similarly after a drought, which has caused the wells to dry up

On the other hand, in villages in which the normal annual rainfall is on the high side, 30 to 40 inches, a drought that merely reduces but does not dry up the wells will be followed by an increase in the incidence of the disease

The **season** when most infections occur is at the end of the hot weather just before the monsoon rains arrive, at this time, the cyclops are present in the largest numbers as the water is shallow and the organic matter is at its highest concentration Further, the concentration of cyclops makes *the water particularly infective at this time of year*

The incubation period is usually about one year, and Rao's collected data show that the curve of the date of onset of symptoms starts to rise in March, reaches its peak in July, and falls again until October, after which it remains at a low level

(c) ***The presence of cyclops***—*Conditions may be suitable for cyclops* 'he temporary or long-standing immu ige communities has been shown to be been washed out by flooding or dried out by drought, it is often several years before the well becomes restocked with cyclops Experiments with animals and even human experiments *(Liston, Turkud, & Bhave, 1913)* suggest that a heavy dose of infected cyclops have to be swallowed to ensure establishment of infection

(d) **Introduction of infection**—Several instances have been reported in which villages in the endemic area have remained free from infection village arrived and infected when a well is used by one ily or the community may remain free from the disease for some time, until a member becomes infected by drinking from another well

PATHOLOGY AND SYMPTOMOLOGY

where it lies with its head near ... extended along the full length

... it lasts about one year, and during this period there are no

all over the body that is intensely irritating There is usually a slight

local signs become more prominent Subsequent attacks, whether in the same season or the following year, tend to be milder, this seems to be against the theory that they are allergic in nature, and suggests rather that the reaction is due to some toxic substance from the worm to which *in time the patient develops some tolerance*

The **local reaction** follows immediately, or is coincident with the general reaction

The **site** of the local reaction is usually the ankle or the foot, but varies according to the circumstances In India, in about 90 per cent of cases the worms point here as these are the parts of the body which commonly come in contact with water, this is probably true of most endemic areas The worm may appear, however, in other parts of the body also, *e g* on the arms, head, neck, chest, back, abdomen, loins, groins, and scrotum, and very rarely on the tongue and eye-lids

Generally, a patient shows only one worm at a time, and when this has discharged its larvæ or has been removed, the patient enjoys a little respite, until the next year when a fresh worm may appear Cases of **multiple infection** are, however, not uncommon A patient may show two or more worms in the same part or in different parts of the body, either ... *In one indi-* ... removed at ... and as many

There is local red induration and vesiculation, and eventually a blister is formed which if the contents are examined will be shown to consist ...

in the subcutaneous tissues the worm protrudes a portion of its uterus that has prolapsed through its mouth or through a rupture in the body wall near the head, this loop of uterus bursts and the larvæ swim out

This hole is kept patent by the worm, which at intervals protrudes its uterus and discharges larvæ, it is an easy point of entry for septic organisms, as the uterus is protruded into a septic environment and drawn *in again so that* ***secondary infection*** *is certain to occur*, but provided the

worm remains alive the local reaction at the mouth of the tunnel in which it *lives is not usually very severe* It may amount to an area of redness and induration about an inch and a half in diameter, tenderness, some lymphangitis, and often a little tenderness of the lymphatic glands in the groin There are seldom any constitutional symptoms

The worm may, however, die before it reaches the surface, if this occurs, or if the worm is broken while being extracted, there will be a sharp local reaction *along the whole length of the site of the dead worm* This may only amount to **cellulitis** which eventually subsides, or there may be **sub-acute abscess formation** at different points along the site of the worm, or the site may become secondarily infected and suppurate, with the severe local and general reaction This **suppuration** may involve important structures, tendon sheaths, joints, or even blood vessels, and cause serious complications, and even death from pyæmia or septicæmia

Finally, when the inflammation subsides, there may be **fibrotic changes** along the whole site of the worm, which may cause scar formation pain and contractures, or the remains of the worm may become calcified and cause painful lumps, chronic arthritis, tenosynovitis, or neuritis

The pathological processes can thus be summarized —

(*i*) A period of invasion lasting up to a year that is not associated with any pathological changes

(*ii*) A general reaction associated with the discharge of some toxic substance by the mature gravid female worm

(*iii*) A local reaction ending in blister formation in the subcutaneous tissues at the point of discharge of these toxic substances

(*iv*) An area of inflammation and induration due to secondary infection at the point of emergence of the worm

(*v*) Cellulitis subacute abscess formation or suppuration along the course of the worm if it dies or is killed

(*vi*) Fibrosis or calcification with various possible complications chronic arthritis synovitis or neuritis

IMMUNITY

There is no evidence that there is any **natural,** race, class, sex or age, immunity, on the other hand, not all those that swallow infected cyclops suffer from the disease

In the human experiment referred to above, only one out of five subjects became infected, and very frequently many of the members of a household whose well is heavily infected will escape infection But Powell (1904) reports an incident *in which 21 members of a party drank water from an infected well, during a visit of two days only*, seven of them became infected and showed symptoms from 11½ to 13 months later

s **acquired,** as many instances
cted year after year, in some
ubjected to infection for a
short time each year while visiting their native villages Again, in a village in Saugor district in India 155 out of a population of 1 095 were infected, of these, 121 had single and 34 *multiple infections* The large percentage of multiple infections in this village certainly does not suggest the development of any special immunity after the first infection *

* A Poisson series would give only about 15 second infections

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The fact that the general reaction shows a tendency to decrease with successive attacks has been referred to above, this suggests development of tolerance to the 'toxin' from the worm

DIAGNOSIS

This will seldom present any difficulty when once the worm has 'presented' and when one suspects the condition, it is often possible to feel the coiled worm under the skin at an earlier date

The diagnosis can be confirmed by the **intradermal test** suggested by G W St C Ramsay (1936), the technique of which is as follows —

Procedure —0 1 c.cm of this is injected intradermally

Result —A weal 2 to 3 c cm in diameter with pseudopodia is considered a positive reaction

The exact position of the worm may be ascertained by injecting it with lipiodol and the x raying the limb The position of calcified worms can also be demonstrated by skiagraphy

There is usually a marked eosinophilia, up to 15 per cent, but this finding is not specific as it occurs in many other helminthic infections

PREVENTION

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Definitive hosts other than man seldom play any important part in the human infection cycle The endless chain man—cyclops—man, can be broken at either link, or the cyclops can be eliminated

For the disease to be transmitted, two elementary principles of sanitation have to be violated, and if either is adhered to, that is, if direct human contact with the drinking water supply is obviated *or* if the water used for drinking is subjected to even the most rudimentary form of filtration or sterilization, the disease will not occur Therefore the most important steps in prevention are **education** and **propaganda**, but, in the endemic areas in India at least, the habits of the people with regard to washing and drinking are deeply ingrained and amount to a quasi-religious ritual, against which it is difficult to make headway

The next measure is **improvement of the water-supply**, that is, the replacement of the unsatisfactory water-supply by a satisfactory one Where possible a pipe supply from a protected source should be installed, but the conversion of step-wells into properly protected draw-wells, or better still into pump-wells, will be efficacious

There will be many instances when from the nature of the terrain or for economic reasons it is not possible to do this, then meas[illegible]

Measures for the **elimination of cyclops** may be (i) physical, (ii) chemical, or (iii) biological

(i) **Physical** —The sudden raising of the temperature of water a few degrees will kill cyclops, therefore the bubbling of steam through a well has been suggested and used as a means of control Unfortunately, the heat that—in practice—it is possible to apply by this means does not kill the eggs of the cyclops, so that the imagines appear in the well again within a few weeks It is therefore not a practicable measure

(ii) **Chemical** —Most chemicals have the same limitation, that is they do not destroy the eggs, except in very high unpracticable concentrations Lime is perhaps the most practicable substance to use as it is often available locally One drachm of lime in one gallon of water (or about one gramme to a litre) will destroy cyclops The gallons of water in a well can be calculated from the formula $4\ 9 \times u^2 \times d$ where u and d are the diameter and depth, respectively, of the well in feet (or *see* p 389)

(iii) **Biological** —Fish will eat both the larvæ and the guinea worm embryos, and Moorthy and Sweet (1936) used this method successfully for controlling guinea-worm, the species they recommended were *Barbus puckelli, ticto, sophore,* and *chola,* and *Rasbora doniconius*

To summarize, control is effected by

(i) education and propaganda
(ii) provision of a piped water supply or at least closure of step-wells or as a temporizing measure by
(iii) destruction of cyclops by physical chemical or biological means

TREATMENT

The aim of treatment should be the destruction of the worm, preferably before it begins to give rise to symptoms, but no drug has yet been shown to effect this In the absence of a specific the treatment must be aimed at ameliorating the clinical manifestations and preventing the more serious complications of the infection

It will be convenient to refer back to the six pathological processes summarized on p 700, and to discuss the treatment in each case, except the first, as in the absence of a specific there is no appropriate treatment at this stage

(ii) **The general reaction** —Fairley and Liston claim that this attack can be cut short by the administration of 10 minims of adrenalin subcutaneously

(iii) **The local reaction** —This cannot be prevented but it can be relieved to some extent by hot and/or cold applications locally

(iv) **The local inflammation at point of emergence of worm** —This [illegible] to some [illegible] he worm [illegible] tage

(*v*) **Cellulitis along the course of the dead worm.**—If it is left, the worm will eventually die and, if its removal is attempted inexpertly, it will break and the remaining portion will die, in either case a nidus for septic infection will be left. Removal of the whole worm is therefore the first consideration under this heading.

Removal of the worm.—The method of removing the worm that has been practised for generations in the villages where the disease occurs is to wind the head of the worm around a small twig or piece of bamboo, and to give the bamboo one turn each day until the whole worm has been removed. The method is frequently successful, but it takes a long time. Manson suggested a modification in which the uterus is first emptied by encouraging oviposition by repeated applications of ice or cold water to the orifice, so that the worm becomes flat and can more easily be removed by the winding process. There is much to be said for this primitive method, if it is carried out carefully and with aseptic precautions.

[illegible]

painlessly under local anæsthesia.

In the event of the worm being broken, or of a portion being left, its absorption can be encouraged by hot fomentations locally and the administration of sulphonamides to prevent or cure sepsis. Should this fail and abscesses form, these will have to be opened in the usual way.

(*vi*) **Sequelæ.**—Finally, if the worms become calcified, or fibrotic cords are formed, that cause pain or interfere with the patient's movements, they must be removed surgically.

PROGNOSIS

[illegible]

sometimes develop fixed joints (ankle or knee) as a result of the prolonged immobilization on account of the inflammation and suppuration associated with the disease, and become cripples for life.

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GNATHOSTOMIASIS

Introduction —Infection with worms of this genus are apparently not very uncommon in animals but up to 1929 only eleven human infections had been reported Maplestone and Bhaduri (1937) in reporting the fourth case from India expressed the opinion that the infection was probably far more common than had been believed hitherto and quoted the findings of Prommas and Daengsvang (1934) and Castens (1935) in Siam (Thailand) There is thus evidence that the infection is more than a medical curiosity and with a greater awareness on the part of the medical profession a wider distribution of the infection may be recognized

The infection is not a serious one and the commonest symptom is fugitive swellings in different parts of the body rather than creeping eruptions that are so frequently associated with this infection in textbooks

Geographical distribution —This appears to be essentially tropical Cases have been reported from Siam (Thailand) India Malaya China Japan and Queensland More than half the reported cases were observed in Siam

In Siam more females than males are affected

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eight rows of hooks arranged ringwise The larvæ measuring less than a millimetre and with only four rings of spines have also been recovered from man The characteristic heads of the adult and larva are shown in figure 178 on the opposite page

The full cycle has not been worked out satisfactorily but it would appear that the true definitive hosts are large carnivores the tiger leopard dog cat and weasel have been found infected in nature The ova are ingested by a crustacean (cyclops) in which they develop into larvæ A second intermediate host appears to be necessary fish frogs and snakes

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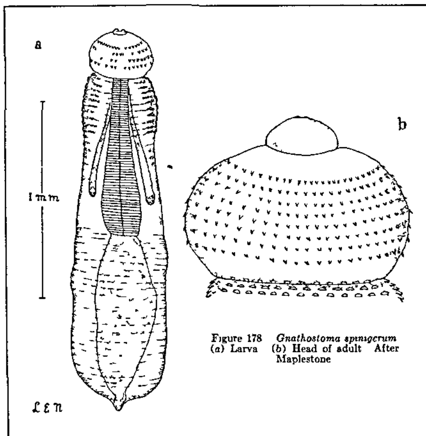


Figure 178 *Gnathostoma spinigerum* (*a*) Larva (*b*) Head of adult After Maplestone

PATHOLOGY AND SYMPTOMATOLOGY

[illegible] in and sub- [illegible] which may [illegible] ay or so, to [illegible] other times the swellings appear within a very short time at points a considerable distance from one another This continues often for several months, but eventually the worm penetrates to a point just below the epidermis and causes a localized cellular reaction, the site of which becomes secondarily infected and an abscess occurs, when this bursts it releases the worm, alive or dead. Or it may be seen before any abscess has formed, in which case it can be removed without difficulty

In a large percentage of cases there has been a history that at some time the worm has migrated in the neck and produced a swelling in the

pharynx that caused dyspnoea and in one case at least the worm has emerged through the mucosa of the pharynx In others, hæmoptysis hæmatemesis, and/or hæmaturia have occurred, without other obvious cause and have not recurred after the worm has emerged or been removed

Only a very few cases have been encountered in which the worm has burrowed horizontally in the skin and produced a serpigenous itchy raised linear eruption, a condition that could be described as 'creeping eruption

DIAGNOSIS

This can only be made with certainty by removing and identifying the worm, but a history of migratory swelling should certainly lead one to suspect this infection, especially if the filarial infections can be excluded

TREATMENT AND PREVENTION

There is no known specific, and treatment consists in removing the worm when it shows itself

Until more is known about the ætiology, no preventive measures can be recommended

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SCHISTOSOMIASIS

Introduction—There are two main clinical forms of schistosomiasis namely the vesical and the intestinal The causal parasites of both forms are trematodes of the genus *Schistosoma* the former is caused by *Schistosoma hæmatobium* (Bilharz 1852) Weinland 1858 and of the latter there are two types which are sufficiently different to warrant separate consideration one caused by *Schistosoma mansoni* Sambon 1907 and the other by *Schistosoma japonicum*, Katsurada, 1904 These parasites are usually known as blood flukes

History.—The Ebers Papyrus referred to hæmaturia that was probably schistosomal in origin and confirmatory evidence of the early existence of this infection in Egypt is provided by Egyptian mummies several thousand years old (20th dynasty)

Bilharz discovered the flukes in the mesenteric veins at an autopsy in Cairo and later he found the eggs in the urine in cases of hæmaturia Cobbold was the first to describe the worm and he gave it the generic name *Bilharzia* but Weinland's name *Schistosoma* has priority and has come to be accepted although the word bilharziasis is still used by some writers for the diseases caused by these flukes

Manson and others suspected that there were two species of schistosome on [illegible]

wi[illegible] two [illegible] [illegible]
was *via* the skin

[illegible] Of the intestinal infections *Schistosoma* [illegible] igtse valley along the south [illegible] g then inland as far north [illegible] especially Leyte and the Celebes and in Japan itself there are five [illegible] ited foci Whereas *S mansoni* is encountered in north Brazil the Guineas Venezuela and Puerto [illegible] Africa along the Congo [illegible] eastern part of the [illegible] Madagascar

The vesical infection—*S hæmatobium*—is distributed widely through Africa, the endemic area extends along the whole of the north coast, up the Nile valley to Abyssinia and down the east coast, taking in the west coast of Madagascar, to Cape Colony throughout which it is endemic, it

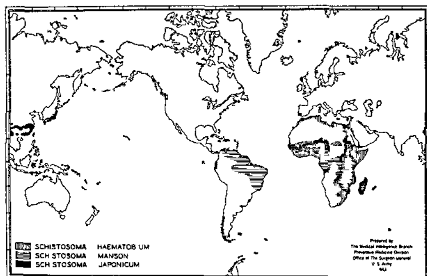


Figure 179 Distribution of Schistosomiasis (Simmons *et al* 1944)

occurs in the tropical countries on the west coast including the Gold Coast, Lake Chad, the Cameroons, and Nigeria, and also at the southern tip of Western Europe, in Spain, and Portugal, and in Palestine, Arabia, and Iraq

ÆTIOLOGY

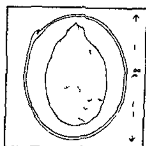
Man is the only important definitive host of *S mansoni* and *S hæmatobium*, but *S japonicum* has many—man, horse, cattle, dog, cat, rats, and mice The intermediate hosts are molluscs of several species and a number of genera

The stages of the parasite that occur in man and his excreta are described on the following page

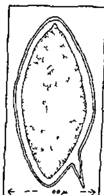
T' [illegible] thi[illegible] They [illegible] two but of about the same breadth The range of measurements, as given by Craig and Faust (1943), and the distinguishing characteristics of the ova of the three species are shown below

	Range in microns	*Special characteristics*
S japonicum	70 to 100 by 50 to 65	Small depression near one pole with m curved hook
S mansoni	114 to 175 by 45 to 68	Prominent lateral spine near one pole
S hæmatobium	112 to 170 by 40 to 70	Distinct spine at one pole

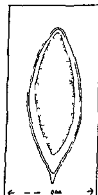
Figure 180 Schistosome eggs



S japonicum



S mansoni



S hæmatobium

The cercariæ.—These are materially the same in the three species, though those of *S japonicum* are smaller They consist of an oval or fuse-shaped body and a forked tail The bodies of the cercariæ of *S mansoni* and *S hæmatobium* average about 200 microns, their breadth is a little less than half their length, the main stem of the tail is a little longer than the body and about 40 microns across and each prong of the forked tail is about 100 microns long When they enter their definitive host, they discard their tails and become **metacercariæ.**

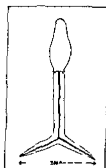


Figure 181 The cercaria of Schistosoma

The adults —The males are shorter and stouter than the females, they measure from 7 to 20 millimetres in length and 0 5 to 1 0 mm in breadth and have two unequal muscular suckers, the smaller one at, and the larger on the ventral aspect near, the anterior end Along its whole length the body of the worm posterior to the suckers is folded ventrally to make the gynæcophoral canal, in which the female is held during fertilization and oviposition

The female is longer and slenderer, it has two suckers in relatively the same position, but they are smaller and not so muscular The uterus, which contains 20 to 30 eggs at a time, opens near the anterior end

The range or average of sizes of the adults of the three species is given on the opposite page

	Size in millimetres	
	Male	*Female*
S japonicum	12 to 20 by 0.50	26 by 0.3
S mansoni	7 to 10 by 1.0	7 to 14 by 0.25
S hæmatobium	*10 to 15 by 1.0*	*20 by 0.25*

Life cycle —In man: the cercariæ are the infective stage They enter through the skin when he bathes or wades in infected water They adhere

vessel and are carried to the right side of the heart, and thence *via* the pulmonary artery they reach the lungs They may also enter through the

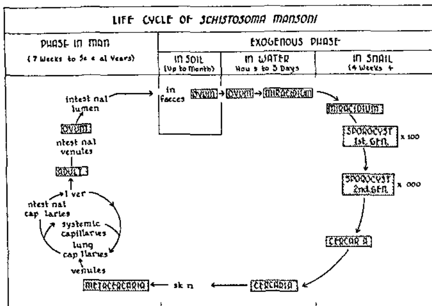


Figure 182

buccal nasal or pharyngeal mucous membranes in persons drinking or washing out their mouths with contaminated water they would not however survive passage through the stomach In the lungs they negotiate the lung capillaries and cross over to the venous side they are carried once more to the heart and thence into the systemic circulation Apparently only those larvæ (meta cercariæ) that get into the right traffic lines and find themselves in one of the mesenteric arteries have any future these on reaching the intestines negotiate a second set of capillaries and crossing over to the portal system reach the liver It is thought possible that some pass through the liver and make another cycle before finally coming to rest in the liver (The larvæ that fail to reach the mesenteric arteries on the first round *probably* do not survive long enough to make another complete circle and negotiate three more sets of capillaries but die and are removed with other blood débris) When the larvæ reach the liver they begin to *feed and develop* they do not however remain here but turn back into the portal vessels and migrate against the blood stream

Up to this point the route taken by all three species is the same, but subsequently their behaviours differ. The larvæ of *S. japonicum* when they reach the superior mesenteric vein turn into the ileo-colic or the colic branches, here, having reached maturity and mated, the female, who is held in firm embrace by the male, stretches her head end, which is directed towards the capillaries, into the venules of the mucous membrane of the small intestine and upper part of the large intestine, and from her vulval opening, near the head, deposits eggs one by one. She then moves to another site and repeats the process. The miracidia within these eggs secrete a lytic substance which percolates through their shells and causes local tissue necrosis and eventually ulceration, from this ulcerated area the ova find their way into the lumen of the gut, and are passed out in the stools.

On the other hand, *S. mansoni* flukes migrate further, into the inferior mesenteric veins, and oviposit in the venules of the mucosa of the descending colon, sigmoid, and rectum, the subsequent course of their ova is the same as those of *S. japonicum*.

Whereas *S. hæmatobium* flukes go further still, and, *via* the hæmorrhoidal plexus, finally reach the vesical and pelvic plexuses where they oviposit into the venules of the mucosa of the bladder, the ova break through into the bladder and are passed in the urine. The course taken by the majority in each infection has been indicated, but there is some overlapping and in *S. japonicum* infection there will be many instances in which the adults migrate in the inferior mesenteric vein and deposit their eggs in the mucosa of the descending colon and rectum, but they never reach the vesical plexus. Conversely, *S. hæmatobium* ova will sometimes be found in the rectum, but are rarely deposited in radicles of the superior mesenteric vein.

First free-living phase.—When the ova, passed in either stools or urine come in contact with water, from each a single ciliated larva (or miracidium) hatches out. These larvæ, which are approximately the size and shape of the ova, are actively motile, but are unable to feed and only live about 16 hours.

In the snail.—They are attracted to certain species of snails (probably by a specific exudate of the latter) whose soft tissues they enter. The miracidia enter the lymphatic vessels of the snails, there they lose their cilia and develop into sporocysts (first generation). The worms develop for 4 to 8 weeks in the snails, mainly in the liver, passing through two sporocyst stages, finally innumerable (up to a quarter of a million) fork-tailed cercariæ burst out of the snail in swarms, daily, over a considerable period, placed at over 60 days by some observers.

Second free-living phase.—These cercariæ, which are only discharged [illegible] days, swim vigour[illegible]ors, but they cannot [illegible] averag[illegible]ing 24 hours and at most three days, [illegible] themselves to the legs of a bathing or [illegible]tive host, discard their tails, and, by [illegible] into his skin to commence a new cycle.

The time factor.—This can best be appreciated by dividing the life cycle into different stages. The migrations of all three species up to the time they reach the liver is about five days and the adults of all three species become mature within three weeks from the time of entry of the lar-

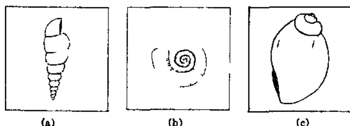
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Variations in the cycle—While the above is the ideal cycle from the point of view of the worms the ova and more rarely the adults will reach a number of other sites Very frequently ova become detached from the intestinal venules and are carried back into the liver this occurs much more constantly in *S japonicum* infection in view of the proximity of the superior mesenteric vein In the latter infection in particular, the ova and even the adult worms may negotiate the liver sinusoids or the collateral portal anastomoses and *via* the systemic circulation again reach the lungs, or they may be carried to and lodge in other organs and tissues *e g* the brain

The intermediate hosts—Craig and Faust (1943) give the following as actual or potential hosts —

For *S hæmatobium Bulinus truncatus* (Egypt Cyrenaica and Tunis), *B forskali* (Mauritius, and possibly Kenya colony) *B tropica* (South



(a) (b) (c)

Figure 183 The snail intermediate hosts of Schistosomes
(a) *Oncomelania* of *S japonicum*
(b) *Planorbis* of *S mansoni*
(c) *Physopsis* of *S hæmatobium*
Actual size of average specimens

Africa), *Physopsis africana* (South Africa and the Belgian Congo) *P globosa* (Sierra Leone, West African Coast northern Nigeria Nyasaland and Rhodesia) *P nasuta* (Kenya Colony) and *Planorbis duforti* (Portugal and Morocco)

For *S japonicum*, *Katayama nosophora* (Japan and along the coast of China), *K formosana* (Formosa), *Oncomelania hupensis* (Yangtse basin), *O hydrobiopsis* (Leyte Philippine Islands)

EPIDEMIOLOGY

The disease occurs mainly amongst populations with a low sanitary standard or where human fæces in a relatively fresh state are used for

manure In some of these populations the infection is very intense, involving as much as 90 percent of the people, as for example in some parts of the Nile valley, and in Egypt as a whole it has been estimated that six million persons, or about half the populations are affected either by *S hæmatobium* or *S mansoni*, whereas in the heavily populated Yangtse valley tens of millions of Chinese are infected

The persons most frequently affected in the endemic areas are fishermen, rice-field workers, washermen or -women, and bathers of any kind including ceremonial (Mohammedan) bathers

Amongst foreign sojourners and visitors, the infection is often contracted by sportsmen, whilst wading through streams or flooded rice fields, by *sailors**, whose duty necessitates their wading in contaminated water, and by pleasure seekers and children in particular, who may wade or bathe in polluted waters

Instances have been reported, *e g* in Egypt and Puerto Rico, where sporadic cases have occurred amongst the general population of towns, and have been traced to cercaria-infected piped water supplies

Persons of all **ages** and **races** are susceptible, but there is frequently a male predominance, and children appear to be very susceptible

The **season** of highest infection in the Nile valley is from February

Factors determining the incidence of the disease

The **essentials** are (i) The sources of infection, man is the sole reservoir of infection for *S hæmatobium*, and probably the only important one for *S mansoni*, although monkeys have been found infected in nature, but for *S japonicum* there are other important sources, for example, cattle, especially water-buffaloes and in Japan field-mice are incriminated, but the relative importance of these non-human sources does not seem to have been estimated

(ii) The presence of snails of certain species to act as intermediate hosts

(iii) Promiscuous defæcation and/or urination, a sanitary system by which waterways are polluted, or the use of human excretions for manure

(iv) The practice of bathing, wading or standing in polluted water, or drinking or washing out the mouth with water taken directly (*i e* without storage *for at least 3 days) from a polluted source*

(v) Climatic (especially temperature) conditions that are favourable to the development of the parasite in the snail and to its survival during its free-living stages

The **extent of the incidence** of the disease present in any locality will depend on the degree to which these factors are in operation In many pla

in

latrines for example, are built over the streams so that urine and fæces fall into them or they are used as the main sewer And in China human excreta are stored in large earthenware jars and used as manure in the rice fields If in such areas suitable snails happen to be present, the incidence of the disease is certain to be very high indeed In other areas, where pollution is a rare incident the disease will be sporadic and unimportant

Where the specific molluscan hosts have only a limited distribution as in certain places in Japan, the disease is localized

From time to time new areas have become infected through snails migrating or being carried into areas where although climatic sanitary and social conditions were already suitable the right species of snails did not previously exist

The male predominance in some places in China for example is due to the fact that boys bathe in canals whereas the girls are not allowed to do so Also on the whole the occupation of the men exposes them more to infection

PATHOLOGY AND SYMPTOMATOLOGY

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There are very considerable variations in the reactions of the individuals to the infections In Egypt, for example a certain degree of tolerance to nfect

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destroyed before they can establish themselves

It is usual in order to facilitate description to divide these pathogenic reactions into stages, this device is a useful one provided it is fully appreciated that not only will one stage run into the next, often imperceptibly, but that *in an endemic area where fresh infections are repeatedly* occurring the stages will be continually overlapping one another

The division which seems the most logical is as follows —

I **The period of invasion and development of the parasite,** up to the time the flukes reach their habitat of choice and develop into the adult stage Clinically this is the incubation period during which however, at the time of the first invasion, mild symptoms of a local nature may occur, these prodromal symptoms are not constant and are almost certainly absent in the native of the endemic area who has been previously infected

II. **The period of egg deposition,** associated with an immediate in- the part *of the host's tissues to* the adult flukes, and possibly to clinical picture associated with this includes a generalized febrile reaction a skin eruption, and liver en largement in all three infections, and usually a little later, as the eggs are extruded into the intestinal lumen, *dysentery*, in *S japonicum* and *S mansoni* infections, or urinary symptoms, as the eggs are extruded into the bladder in *S hæmatobium* infection

III. **Period of fibrosis and attempts at tissue repair.**—In this stage, the most serious and varied complications, with irreparable damage to many organs, occur

The pathology and symptomatology are described separately below, events, without separation into the divisions come Further, in of *the three different infections* re the courses of the parasites diverge

PATHOLOGY

Skin.—At their point of entry, the meta-cercariæ usually produce no gross pathological lesions, but in experimental infections minute petechiæ can sometimes be seen with a hand-lens However, after a short time when they have penetrated into the skin proper, they call forth a local tissue reaction which destroys a certain proportion of the cercariæ, and their bodies, then acting as foreign protein, give rise to local allergic manifesta tions—urticaria and œdema This reaction is much more noticeable in foreigners than amongst the local native population

It is of interest that this skin reaction is also much more servere and is likely to develop into a dermatitis in the case of the cercariæ of schis tosomes that are not the natural parasites of man and fail to establish themselves in his tissues, *e g Cercaria elvæ*, reported in the United States (Lake Michigan), and *Cercaria ocellata* from Wales and elsewhere in Europe, which cause cercarial dermatitis but no visceral infection *In these* cases, the meta-cercariæ are probably all destroyed locally and give rise to the maximum reaction

Lungs—Again, the passage of the lung capillaries is apparently accomplished without causing much local reaction, by the majority of the larvæ, but others break through into the alveoli where they may cause hæmorrhages and local reactions in the submucosa of the alveolar walls ... *pneu* tensive

General reaction—When, however the larvæ reach the portal vessels and develop into adults, they cause a generalized reaction that is frequently the first evidence of the disease This reaction seldom appears before the end of the third week and is sometimes delayed for as long as three months, it is caused by *metabolites from the adult parasites, some of* which are probably associated with the parturition of the females This reaction occurs only during the invasion of the first crop of parasites or, if it is repeated, it is much milder, so that apparently the individual becomes desensitized to the toxic agent, whatever it is The reaction is associated with *hyperæmia and hyperplasia of the* liver and often of the spleen, and a very marked eosinophilia, 10 000 per c cm (*circa* 60 per cent) or more

Local reaction to the ova—Where this reaction takes place will naturally depend on where the eggs are deposited and this will vary with the species of the infecting flukes (*vide supra*)

c

the venule and often abscess formation Around these abscesses giant cells and fibroblasts appear This process occurs in the mucosa and sub

the muscularis into the sub mucosal papillomatous growths

Th

stools

The eggs are also deposited in the muscular coats where they produce the same infiltration abscess formation and fibrosis and sometimes they calcify so that in time the whole wall of the bowel may become a thickened and hard more or less functionless tube These deep ulcers with their bases in the muscular layers may in time heal leaving scars that later contract and may cause obstruction In these later stages any dysentery that occurs will usually be associated with intestinal strictures and the diarrhœa which is a common terminal event will be due to mucosal dysfunction and malabsorption

Finally the serous coat may be involved there will be a fibrinous exudate on the surface which results in adhesions forming between loops of viscera The mesentery and the retroperitoneal tissues are also involved as well as the the lymphatic glands in both these situations Subsequent fibrosis and contracture will tend to produce further intestinal complications

A large number of eggs find their way back to the liver probably be
vould be difficult
s In the liver
he eggs are sur
and are even
the metabolites
from the adult flukes lead to the production of at first hypertrophic and later cirrhotic changes in the liver Ascites and other sequelæ of portal cirrhosis will develop and later when the cirrhotic changes involve the biliary canaliculi jaundice Thrombosis of the portal vein is not an uncommon sequel

These changes in the liver will lead to passive congestion then hypertrophy and finally fibrosis in the spleen so that the organ may become

immense It may contain a few ova, but these are usually insufficient to account for the extreme enlargement which is mainly secondary to the liver involvement In some cases the splenic vein is thrombosed

In both the liver and the spleen, the reticulo endothelial cells contain large quantities of hæmatin from the changed blood excreted by the flukes

Sometimes eggs are found in the lungs, brain and spinal cord, kidney and other organs and tissues, where they produce similar changes

In *S mansoni* infections, a very similar series of changes occur, except that the brunt falls on the lower end of the colon, the descending colon,

bowel lesions appear to be absent and only the hepatic and splenic changes are found

In *S hæmatobium* infections, *most of the eggs are laid in the radicles* of the vesical and pelvic venous plexuses, but occasionally the adults wan- …oin, scrotum, and perineum, …in these areas These eggs …they reach water would be …r the eggs are placed in the venules of the mucosa and submucosa and cause parallel changes to those …may burst into the lumen of the bladder, so that …formed … Ulcers …l ovum, …of the …of …on

…ll of the bladder and in …per layers of the bladder …surrounded by fibrous tissue, they are later either replaced by fibrous whorls or they become calcified If there are many eggs, the bladder is eventually converted into a rigid and useless bag Eggs are also deposited in the lower end of the …and may in time cause an obstruction and hydronephrosis, and also …surrounding this, where they may cause a …nis, and later, if the eggs become calcified, …part of this organ may occur They are …they cause hypertrophy, and, in the pelvis, …d and the lymph flow obstructed, so that …lia and/or a proliferating warty condition around the anus may …en the eggs are deposited in the venules of the skin of the groin, scrotum, and perineum, here they cause a papular eruption which may become pustular Viable eggs can be found in a smear made from scrapings from these eruptions

A few eggs may be deposited in the mucosa of the rectum and be extruded *in the fæces* as in the case of the other blood flukes, but seldom

elsewhere in the intestinal canal except apparently the vermiform appendix (in one series in Nigeria, 57 per cent of the appendices removed contained ova)

In the later stages secondary infection of the bladder is almost the rule, this infection will often ascend to the kidneys and cause pyelitis and pyelonephrosis

Eggs frequently reach the systemic circulation in the infection with this species on account of the fact that the venous return from the areas where they are most frequently deposited is *via* the inferior vena cava, the eggs are usually held up in the lung but sometimes get through to other organs and tissues *e g* the brain and cord In the lungs, an interstitial pneumonitis is frequently caused

The blood picture—In the early stages, as already noted, there is a marked eosinophilia and usually little change in the hæmoglobin percentage or red cells, in the second stage, anæmia tends to develop in all three infections and although there may still be a relative eosinophil increase,

[illegible]

reduction in—eosinophils, but sometimes a polymorphonuclear leucocytosis as a result of secondary bacterial infections, though as a terminal event this also will fail

SYMPTOMATOLOGY

Schistosomal dermatitis—At the time of infection, as the water dries on the skin there may be a tingling sensation which is shortly followed by the development of small urticarial weals at the sites of entry of the cer-[illegible]

Th[illegible] a result of infection with any of the [illegible] it is not constant and is apparently [illegible] (only in 10 per cent of the American [illegible] above it occurs much more constantly [illegible]ie schistosome that does not establish itself in man The syndrome is known as 'swimmers itch in the United States (Cort, 1928) and Canada (McLeod, 1940) where it commonly occurs amongst bathers in the big lakes

The febrile attack—This occurs between the end of the third week and the end of the third month It has been reported as early as the fifth day in *S japonicum* infection, but the experience of others and experimental work suggest that these reports of the very early occurrence of the febrile attack should be [illegible]

[illegible] is not so well defined or constant The onset may be gradual or sudden The fever usually rises each evening to about 102° and then falls to normal or the 99° line towards morning (figure 184) There are usually chills, and often an actual rigor followed by profuse perspiration during the night The fever is accompanied by malaise, anorexia, pains in the back and along

the nerves of the limbs, and sometimes by a cough, nausea and vomiting abdominal discomfort and diarrhœa

At the *same time or within a day or two, an extensive* urticarial rash

of the mouth and throat, so that it seems possible that most of the symptoms may be associated with similar local reactions e g the cough and the diarrhœa may be due to patches of œdema in the lung—which can sometimes be identified by auscultation—and urticarial swellings of the mucous membrane of the intestine, respectively The urticaria as is usual, is associated with intense irritation, and dermatographia is often observed

Figure 184 The fever in *S japonicum* infection

The

febrile attack is no
symptoms During
expected

The liver is usually enlarged painful, and tender, and the spleen palpable There may be cerebral symptoms, and in heavy infections death will sometimes occur at this stage

The period of egg extrusion and tissue proliferation—At this point the symptomatologies of the three infections diverge and will have to be considered separately

***S japonicum* infection**—The first signs may appear simultaneously with the febrile attack or after a few weeks interval There will be pain and tenderness in the epigastrium and in
the passage of frequent dysenteric stoo
found very often with pus and other

side and
tion will be left except in the lightest infections However,
infections and in the cases of repeated infections that are the rule in highly

endemic areas, the process will be more or less continuous, with a few quiescent periods, during which the symptoms recur immediately when the patient returns to work or otherwise exerts himself, and after a few years (3 to 5 years is sometimes the interval mentioned but it must be very variable) the condition will pass imperceptibly into the next stage

In **the final stage,** there is increasing emaciation, debility, anæmia, and dyspnoea Children show stunted growth and intellectual retardation The dysenteric condition may continue, but usually takes on the features of chronic ulcerative colitis, there may be some intestinal obstruction with distension of the upper part of the intestinal tract and alternating constipation and diarrhœa The liver may enlarge further, but usually becomes hard and very fibrotic and tends to contract The spleen however shows complementary enlargement and may reach the symphysis pubis or the right iliac crest and it also becomes very hard There are frequently extensive ascites, distension of the abdominal veins, and hæmatemesis results of portal obstruction The emaciation is profound on account of absorption failure in the upper intestinal tract and liver dysfunction, the patient usually develops a sub-icteric tint and sometimes frank jaundice Jacksonian epilepsy, hemiplegia, paraplegia and blindness have followed the deposition of the eggs into the brain, the cord, or the optic nerve

Death may occur from inanition secondary infections, such as pneumonia which may be encouraged by the reaction caused by the ova in the lung, hæmorrhages, or intestinal obstruction or suddenly as a result of the local reaction to the ova in the heart or brain

***S mansoni* infection** —The course of events is very similar to that in *S japonicum* infection, but on the whole the course is not usually so severe, and more symptoms are referable to the rectum For example,

is not interfered with to the same extent, the pathogenesis being mainly in the large bowel

In Egypt, hepatic and splenic enlargement sometimes occur without any corresponding intestinal pathogenesis (Girges, 1934) and, conversely in Puerto Rico intestinal lesions are reported without any liver involvement (Pons 1937)

***S hæmatobium* infection** The first symptom may be an irritating papular eruption in the groin, scrotum and/or perineum which goes on to pustular formation, but this may not be noticed by the less sensitive patient The urinary symptoms usually do not appear until several months after infection took place and in some cases even several years The first

come blocked as a result of peri urethritic inflammatory reaction to the deposited ova, and increasing difficulty in micturition alternating with incontinence will give place to complete suppression, or urinary fistulæ may develop Infection of the bladder soon becomes inevitable, and this in-

fection will spread to the kidney There will be a return of fever, with emaciation and increasing weakness, soon followed by death

In more chronic cases the polypoid growths in the bladder undergo malignant changes, and carcinoma of the bladder is a very common complication in Egypt

Besides symptoms directly referable to the bladder involvement, the uterus and vagina may be involved in women and the penis in men, and there may also develop an elephantoid condition of the labia or scrotum, as a result of blocking of the lymphatics in the pelvis ' A polypoid mass may develop around the anus, and the rectum may also be involved, with the development of fissures, fistulæ and bleeding hæmorrhoids

Acute appendicitis may result from deposition of eggs in the appendicular mucosa, but the latter incident, which is apparently very common in endemic areas, does not necessarily produce acute symptoms

Bronchial asthma is a common result of schistosomiasis in Egypt and so also is interstitial pneumonitis

In this infection, there are few symptoms referable to the liver, or spleen, but occasionally the ova reach other organs, as in the case of the other schistosomes, and may rarely produce symptoms

DIAGNOSIS

This must be made (*a*) from the history of the patient, including past symptomatology, (*b*) from the clinical picture, including cystoscopy, sigmoidoscopy, and blood examination, (*c*) by immunological reactions, and (*d*) by the finding of the ova

(*a*) **The history of the patient** —In the endemic areas, the fact of residence in these areas is usually sufficient presumptive evidence but this

([illegible] *In the case* *of S* [illegible] nd even in *S* *hæma* [illegible] obtained by sigmoidoscopic examination, pseudo-tubercles, sessile papillomata and pedunculated polypi and ulcers can be recognised, and from the latter, material can be obtained in which the ova may be found

By digital examination of the rectum the abscesses and pseudo tubercles in the bowel wall and also in the posterior wall of the bladder may be felt

[illegible]

of [illegible]
ish [illegible]
the [illegible] surrounded by areas of hyperæmia,
and [illegible] hes In the early stages of the in-

fection, some information will be obtained from the **blood picture.** There are probably few diseases in which such a striking eosinophilia will be found, as during the early generalized reaction to the infection On the other hand many helminthic infections will cause a very marked eosin-

The intradermal test with a similar alcohol extracted saline antigenic preparation on the lines of the Casoni reaction in hydatid has been recommended, but it is not so reliable as the complement deviation test

(*d*) **Finding of the ova in stools or urine**—The parasitic diagnosis is in many ways the most satisfactory, as it enables a definite diagnosis of the infecting species to be made but it will not be positive until the disease is well into the second stage, and there are advantages in an earlier diagnosis Further, unless the ova in the stools are very numerous they are likely to be overlooked and some form of concentration method is advisable

Craig and Faust (*loc cit*) recommend a sedimentation method

ment in a conical
ed the process is
the miracidia will
with a low power
lens for the ova

An alternative method is to place the sediment in a tall glass cylinder full of water and leave it for 24 hours the ciliated miracidia will hatch out and can be seen by means of a hand lens swimming near the surface of the water

As indicated above, a more certain method of finding the ova is to take a swab specimen directly from the ulcer during a sigmoidoscopic examination

The finding of ova of *S hæmatobium* in the urine presents less difficulty, if the urine is allowed to sediment in a conical glass, although they may only appear intermittently In this infection also ova will sometimes be found in the stools

Thus **to summarize,** in the early stages a diagnosis must depend on the history, the clinical picture, and the complement deviation test, in the middle period cystoscopic or sigmoidoscopic examination and the finding of the ova in stools or urine will be additional methods and in the final,

the nature of the disease

PREVENTION

The reader is referred back to p 714, where the essentials for the occurrence of the disease are given No action can be taken under the fifth of these headings—climatic conditions, but each of the other four indicate

where the transmission cycle can be attacked We will consider the subject under four headings which correspond to the first four essentials

(*a*) **The elimination of the source of infection** —The source of infection could theoretically be eliminated in the cases of *S hæmatobium* and *S mansoni* infections, by systematic treatment of the population as man is the only important source This method will be less effective in the case of *S japonicum* infection as there are other definitive hosts In certain areas this method has been practised in conjunction with other procedures with some evidence of success as a means of *reducing* the *source of infection but without any real expectation of eliminating it* entirely

The educational value of an organized treatment campaign is very considerable even the most ignorant natives of the endemic areas appreciate the value of treatment and are likely to take more notice of advice regarding prevention given by the doctors who can cure them

The destruction *of rodents and other possible alternative hosts of S japonicum* should be considered under this heading but the relative importance of these other hosts has not yet been properly assessed

(*b*) **Destruction of molluscan intermediate hosts** —Theoretically this method promises well in practice except for isolated and limited bodies of water it has been a failure Periodic drying of irrigation canals reduces the snails but some burrow in the soil and reappear later The de*struction of snails by chemical means e g 1 in 500 000 copper sulphate* will lead to their temporary disappearance but unless the body of water is an isolated one rapid reinfestation will occur this has been the experience in Egypt

For small isolated bodies of water when immediate snail elimination is required the introduction of copper sulphate sufficient to make a final solution of 1 in 200 000 to 1 in 500 000 should be applied this can be done *by placing the copper sulphate in a bag and towing it behind a* small boat backwards and forwards through the water preferably after preliminary removal of aquatic vegetation

(*c*) **Prevention of contamination of water with human or other host's, fæces and urine** —All workers are agreed that this is the pivotal point of prevention but putting it into practice presents difficulties that are usually immediately insuperable

In the endemic cases in Africa including North Africa and the Nile delta most of the population involved are ignorant peasants with not very high sanitary standards In the dry parts of the country where there is little rain to wash surface contaminants into the waterways contamination of water must be deliberate and due to inappreciation of the significance of the act it should therefore be easier to prevent under these conditions than in wet countries where fæces and urine deposited promiscuously *on dry* land will frequently be washed into water

The introduction of proper sanitary systems and education and propaganda are the only solution but it will be generations before they are fully effective

Where domestic animals are sources of infection they should as far as possible be kept away from the vicinity of snail infested water

In China, an additional problem has to be faced There, human excreta are stored in *kangs* and later used as manure If fæces and urine are undiluted with water, eggs will only survive in these *kangs*, which act as septic tanks for three weeks, so that if several *kangs* are kept and used in rotation and none is used within three weeks of the last addition of fresh fæces, the material should be free of eggs and miracidia The addition of an antiseptic, such as sodium cyanide, that might add to the manurial value of the contents has also been suggested as a preventive measure

(*d*) **Obviation of contact with contaminated water** —In the case of the individual foreign
culties and the knowle
is necessary The sp
endemic areas In th
not apparently penetrate the skin under water, bathing in some antiseptic solution immediately on coming out of the infected water should prevent infection Experimentally, it has been shown that cercariæ go beyond the reach of alcohol applied to the skin within about ten minutes, so that any delay would nullify the effect of the procedure

The case of the soldier or sailor under combat conditions is however different Engineers who habitually have to spend a long time in the water (*e g* while building bridges) should be provided with high wading overalls but these would be too cumbersome for the infantry Data are not yet available, but it seems very probable that if the clothing were of a sufficiently fine weave, or if it were impregnated with copper sulphate

In the case of the native, his livelihood will often depend on entering water at frequent intervals, and prevention at this juncture of the transmission cycle seems to be out of the question 'Nursery' rice fields are a very potent source of danger as these are heavily manured, as far as possible children, who are particularly susceptible to infection, should be kept out of these fields

Under this heading must be considered the treatment of water that is to be used for household purposes The cercariæ will go through a 30-

In areas where some domestic animal, *e g* the water buffalo, acts as a reservoir of infection, every effort should be made to prevent such animals entering infected water to initiate or renew their infections

TREATMENT

Treatment must be considered under two headings, specific and symptomatic

Specific Treatment

History—The first successful specific treatment was carried out by Christopherson in 1918 who at the suggestion of McDonagh, used intravenous tartar emetic that had been in use for several years in the treatment of leishmaniasis

Antimony preparations.—The first drugs to be used were potassium and sodium antimony tartrate and many believe that even today they are the most effective The sodium salt is apparently the less toxic They are given in 2 per cent solution in normal saline made with distilled water The solutions must be made freshly or some preservative, such as 0 5 per cent phenol, added in which case the solution can be kept at least two weeks It is sterilized by being brought to the boiling point twice, prolonged boiling or
cule It is given
three times a wee
the dose should be increased to 3 c cm, 4 c cm, 5 c cm and 6 c cm, if the patient appears to be able to tolerate it The principal signs of intolerance are coughing, vomiting, and joint pains When these occur it may be necessary to increase the doses by only 0 5 c cm or even to repeat the last dose until tolerance is established A total of at least 2 grammes should be the aim, which, if all goes well, will necessitate 18 injections *over a period of 5 or 6 weeks*

Children are given proportionately smaller doses

It appears to be necessary to push the dosage of this drug a little higher than in the case of kala-azar (*quod vide*, p 168) There is some difference in the tolerance of this drug by different nationals, Egyptians appear to tolerate the larger doses well, whereas in Venezuela the intolerance rate is high and it is sometimes necessary to drop the strength of the solution to 1 per cent

Fouadin (or stibophen), a trivalent aromatic compound of antimony, is less toxic and also can be given intramuscularly It is, in the experience of some workers, more effective than the pentavalent salts of antimony, but, in that of others, it has proved less effective Fouadin is marketed as a 6 per cent solution in ampoules The dosage is 1 5 c cm, 3 5 c cm, and *5 0 c cm, on the first three days, followed by 5 c cm, on alternate days* until a total dose of 45 c cm, has been given (Khalil and Betache, 1930)

The latest recruit to the antimony preparations is the well-advertised *but not very extensively* tested, anthiomaline—lithium antimony thiomalate (Baugé, 1941) Two cubic centimetres of a 6 per cent solution are given *on alternate days, the course is 10 injections*

Emetine has also been recommended, but to be effective it has to be given in dangerous doses, it should therefore be reserved for those cases in which antimony has failed

Results of specific treatment—The stage of the disease appears to be more important than the species of the infecting schistosome The treatment will be effective only during the active stages of the infection, that is, before the third stage of the disease is established and irreparable damage *has been done* In the earlier stages of the disease, the improvement is often immediate The action appears to be on all stages of the worm including the ova, as the ova that are excreted after treatment has been well established are usually dead later, no more appear, indicating the death of the adult

Symptomatic Treatment

stages of hepatic involvement in the visceral infections, and such surgical procedures as appendectomy, splenectomy, and removal of polypoid growths

PROGNOSIS

In the vesical infection the large majority of the attacks are mild and almost symptomless In these and in all early cases the response to specific treatment is good, but in advanced chronic cases, when there is much involvement of the bladder wall and pelvic tissues, and when secondary infection has occurred, the prospects are poor and the patient will almost certainly die within a short time of sepsis or concurrent disease

Similarly, in the visceral infections, there will be many symptomless infections The course of the disease is on the whole slower and less severe in *S mansoni* than in *S japonicum* infection In both, response to treatment in the early stages is good, but once the liver becomes cirrhotic, death within a year or so becomes inevitable Even in the absence of liver cirrhosis, many patients with extensive bowel lesions will die of malnutrition and exhaustion

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OTHER FLUKE INFECTIONS

CLONORCHIASIS

PARAGONIMIASIS

FASCIOLOPSIASIS

CLONORCHIASIS

Historical—This fluke was first discovered in the bile-ducts of a Chinese carpenter who died in the Medical College Hospital in Calcutta in 1874 It was described by McConnell (1875) The life cycle of the parasite was worked out by several Japanese parasitologists and the most important recent work on the subject was carried out by Faust and Khaw (1927)

EPIDEMIOLOGY

Geographical distribution—The infection is endemic in China Korea Japan Formosa and French Indo China Its brief appearance in Hawaii was probably due to the consumption of fish imported from Japan

Incidence—As the infection of man is dependent entirely on the consumption of under cooked or uncooked fish the disease will be most prevalent in those groups of the population in which this practice is most common In Canton for example where fish is expensive the disease is common amongst better class males who eat in restaurants where specially prepared
class members
ereas in certain
y the poor its

It is uncommon that symptoms due to this infection will occur in children on account of the time it takes for the pathogenesis to develop

ÆTIOLOGY

The causal parasite—Two phases of the parasite are likely to be encountered in man the adult in the bile passages and the ova in the stools

The **adult** of *Clonorchis sinensis* (Cobbold 1875) Looss 1907, is a semi transparent leaf shaped fluke measuring from 10 to 25 millimetres in length by 2 to 3 mm in breadth slightly broader and more rounded at its posterior end

The **eggs** are ovoid and flask shaped with a distinct shoulder around the aperture over which the operculum lies At the opposite pole there is a small knob or hook The eggs measure 27 to 35 microns by 11 5 to 19 5 microns (figure 185) They contain a fully developed miracidium

Life cycle—The ova are discharged in the fæces by the definitive mammalian host and are taken up by the intermediate host a snail of the appropriate species, here the miracidium hatches out and the parasite passes th

extrude ...

..., and
The
vers a

Hosts.—Man is an important definitive host and helps to maintain the cycle, but dogs, cats, badgers, weasels, martens, and minks and several other carnivora are also definitive hosts in nature

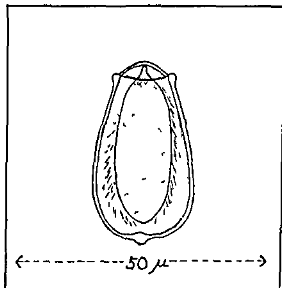


Figure 185 The egg of *Clonorchis sinensis*

Species of several genera of snails act as intermediate hosts, *Parafossarulus*, *Bithynia*, and *Melania*, and some 40 species of fish have been found infected

PATHOLOGY

The pathological reactions to the presence of these flukes appear to result from toxic substances secreted by the adult worms, from impaction of clumps of sticky eggs in small bile ducts, and possibly from mechanical damage by the adults themselves All the primary changes occur in the liver, except in very heavy infections when the pancreas is involved, all other pathological changes are secondary to liver damage

Fibrosis and thickening of the walls of the bile passages throughout the whole organ with proliferation of bile-ducts in certain areas, and both intralobular and interlobular cirrhosis are described Hoeppli (1933) found extensive changes in 66 post mortem specimens from patients who died from other causes (In view of recent work that has shown that extensive liver changes may result from dietary deficiency, it would be well to accept his conclusions as to responsibility of the parasite in all these cases, with caution)

SYMPTOMATOLOGY

The majority of mild infections are apparently entirely symptomless.

The symptoms are not very characteristic and indicate liver damage generally rather than any specific damage caused by this parasite

Gastro-intestinal disturbances are common, diarrhœa and irregularities of appetite, a sense of fullness in the liver region and liver enlargement periodic jaundice, and later ascites, hæmorrhages and other results of cirrhosis often occur

Cardiac and nervous symptoms are also decribed

There is usually a leucocytosis and a slight eosinophilia

DIAGNOSIS

The only satisfactory method of diagnosis is by the finding and identification of the eggs in the stools Floatation methods should not be used Ova may also be recovered by duodenal catheterization

PREVENTION

Personal prophylaxis can be achieved by avoiding the consumption of under- or uncooked fish Education and propaganda pointing out the danger of this practice in the endemic areas should be undertaken

As man is an important source of infection, sanitary disposal of [illegible] irely [illegible] con- [illegible] will [illegible]

A third method of control is by the destruction of snails (*vide* SCHISTOSOMIASIS) where this is possible

TREATMENT

There is no entirely satisfactory specific for this infection, but good results have been claimed for gentian violet (*see* p 632) Other drugs used with apparent success are the antimony preparations, sodium antimony tartrate, and fouadin, and the gold preparation solganol-B

PROGNOSIS

[illegible]

Heavy infections undoubtedly cause irreparable liver damage and shorten the patient's life In cirrhosis from whatever cause, the prognosis is bad

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PARAGONIMIASIS

[illegible] tion [illegible] Chir [illegible] port [illegible] Cameroons in New Guinea, and, in the western hemisphere, in Peru, Venezuela, and Brazil

Infection amongst mammals covers a much wider area including [illegible] prevalent.

ÆTIOLOGY

The causal parasite—*Paragonimus westermani* (Kerbert, 1878) Braun, 1899, is a relatively thick (3 to 5 millimetres) ovoid fluke, meas-

uring 7 to 12 mm in length by 4 to 6 mm in breadth slightly broader anteriorly than posteriorly with two suckers one placed at the anterior end and the other in the middle line slightly anterior to the centre of the body of the fluke

The eggs measure from 80 to 120 microns in length by 40 to 60 in breadth they are oval in shape and have a wide opening at one end over which there is a *flattened operculum*

The life cycle—The egg passed by the definitive host remains in water for several weeks before it is mature the time depends mainly on the temperature The miracidium emerges and enters a suitable snail after an interval of several weeks during which the parasite passes through several stages it emerges from the snail as a free swimming cercaria this cercaria actively enters the soft parts of a second intermediate host a crustacean and in this crustacean it encysts When the crustacean is eaten by the definitive host (e g man) the metacercaria is released from its capsule by the time it reaches the duodenum it penetrates the wall of the duodenum migrates through the diaphragm and pleural cavity to reach the lung* In a small pocket in the lung which is formed around the parasite it develops into an adult and when mature extrudes eggs that are coughed up by the host and the cycle is complete If swallowed the eggs remain viable and are passed out with the fæces The phase in the definitive host takes several weeks to complete

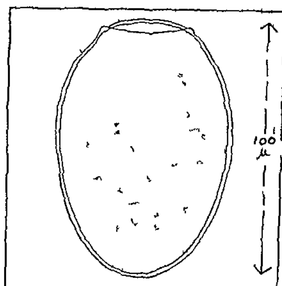


Figure 186 The egg of *Paragonimus westermani*

Other organs or tissues in which the metacercariæ may come to rest are the liver spleen brain peritoneum testes prostate epididymis muscles and skin

Hosts—Besides man the tiger panther leopard wild cat domestic cat wolf fox dog mongoose muskrat and rat can act as definitive hosts

Melania libertina is said to be the commonest snail intermediate host but *Ampullaria luteostoma* and other species of *Melania* are also potential hosts

A number of crustaceans of the genera *Astacus Eriocheir Potamon* and others have been found infected and other crustaceans are probably capable of acting as the second intermediate hosts

* It is not clear why metacercariæ should take this direct but somewhat unusual route rather than the more biological one via the lymphatics and systemic blood which would take them straight to the lungs

PATHOLOGY

In the lung there is a sharp cellular reaction to the presence of the parasite consisting mainly of polymorphonuclear leucocytes and eosinophils later, fibroblasts appear and eventually a thick band of fibrous tissue is laid down around the worm. Within this fibrous capsule besides the worm there is a mass of reddish brown purulent material in which the eggs of the worm can be found. Periodically these abscess like cavities communicate with an adjoining bronchiole and the fluid contents is discharged into a bronchus and coughed up or swallowed by the patient The worm however remains and the process is repeated Sometimes several of these cavities or tunnels coalesce and a comparatively large cavity is formed

In other organs and tissues where the larvæ may come to rest and the adult worms develop a similar tissue reaction and 'abscess' formation occurs In any of these places a secondary infection may take place and the fibrous capsule and its contents be replaced by an ordinary abscess

SYMPTOMATOLOGY

This will naturally depend on the main site of the encysted worms [illegible] like that of pulmonary [illegible] ver There may be an [illegible] paroxysms may occur [illegible] The reddish-brown sputum that the patient coughs up is suggestive of the rusty sputum of pneumonia *There may be a hæmorrhage after a particularly violent fit of* coughing In uncomplicated cases physical signs are few, but there are usually râles However, complications such as broncho pneumonia pleurisy and empyema are not uncommon

In the brain, the encysted parasites may cause Jacksonian epilepsy and other cerebral symptoms in the liver, they may cause liver pain and enlargement, in the intestinal walls they may cause abdominal pain and gastro intestinal disturbances, in the prostate epididymes and testes, they may cause pain and swelling, and in the skin they may discharge at the surface and cause an open ulcer

DIAGNOSIS

This is dependent almost entirely on the finding and identification of the eggs, either in the sputum or in the stools In the latter case they may have come from cysts in the intestinal wall that burst into the lumen of the intestine, or from the lung, having been coughed up and swallowed.

X-ray examination has proved disappointing as a diagnostic procedure

A complement fixation test has given a high percentage of positive results

PREVENTION

It will be apparent from the ætiology of the disease that there are several points at which the transmission cycle could be attacked, but in none of these cases would it be possible to devise any practicable measures

By means of education and propaganda and of necessary legislation, the practice of eating uncooked crustaceans should be stopped, but even this will not reduce the potential danger, as the cycle can probably be

maintained satisfactorily through other mammalian hosts, so that any future relaxation would probably again lead to the development of fresh cases

TREATMENT

Practically the only treatment for which any success has been claimed is with emetine Large doses, bordering on toxic doses, must be given to be of any value Doses of half a grain three times daily for at least a week have been recommended, and it is claimed that better results are obtained if this is combined with *prontosil in full dose*

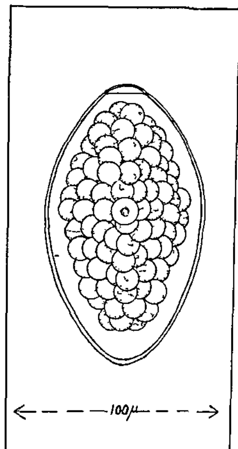


Figure 187 The egg of *Fasciolopsis buski*

PROGNOSIS

This is usually fairly good, except in the case of very heavy infections or in those cases in which serious complications have already developed

FASCIOLOPSIASIS

Introduction — This is a disease caused by the large intestinal fluke, *Fasciolopsis buski* (Lankaster, 1857), Odhner, 1902, that was first observed by Busk in 1843 in the duodenum *of an Indian lascar who died* in London The pig is also a definitive host and probably the main reservoir of infection, the life cycle of this fluke includes stages in a snail and in an aquatic plant, and the *fluke establishes itself in* man when he eats the latter

EPIDEMIOLOGY

This infection occurs in India (Bengal and Assam), southern and central China, Indo China and Siam Formosa, the Dutch East Indies and Borneo and other East Indian islands It has not been reported from the other continents

It occurs amongst the poorer members of the native populations of the endemic areas and mainly amongst children, who ingest the encysted embryos while they are removing with their teeth the outer covering of the edible portion of certain aquatic plants

ÆTIOLOGY

Fasciolopsis buski is a large broad hermaphroditic fluke, from 20 to 75 microns long by 8 to 20 microns across It has one oral sucker at its anterior end The eggs are large, 130 to 140 by 80 to 85 microns, golden brown in colour, and ovoidal in shape (*see* figure 187) (Plate A, fig *16)*

The shell is thin and has a small operculum (a lid like structure) at one end In the immature egg the contained protoplasm is divided into a large number of regular globular masses which almost fill the shell

Life cycle—Man is infected by consuming raw aquatic vegetation, the parasite gaining entry in an encysted larval stage Excystation oc-

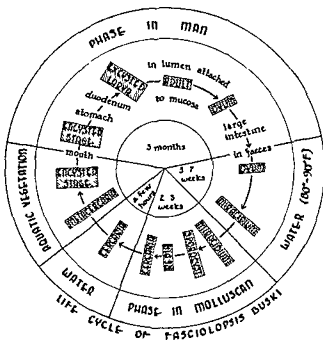


Figure 188

reaching the water mature in from three to seven weeks at a favourable temperature (80° F.–90° F) The miracidium that emerges from the mature egg swims ... of a suitable snail ... genera have been ... a few weeks cercariæ ... free swimming parasites they penetrate the seed pods and roots of certain aquatic plants where they encyst. In Bengal and Assam, *Trapa bicornis* and in China *T natans* and the water chestnut *Eliocharis tuberosa* are commonly infected, these are ingested by man and the cycle is complete.

PATHOLOGY AND SYMPTOMATOLOGY

Within man the parasite lives only in the intestinal canal, but it is capable of causing considerable local damage to the intestinal mucosa at the point of its attachment. There is also evidence that it secretes a toxin

that is injected into or absorbed by the host There is an area of inflammation around the point of attachment of the worm the centre of which later sometimes becomes necrotic, ulcerates, and bleeds, or an abscess may develop in the mucosa and eventually rupture into the intestinal lumen

The fully-developed syndrome is that of a true dysentery, with severe abdominal pain, blood and pus in the stools, and considerable toxæmia and prostration In heavy infections, particularly in children, the toxæmia predominates and is associated with œdema of the face, trunk and legs, and ascites, and may result in the death of the child Milder infections will cause little more than abdominal discomfort, a toxic diarrhœa, and slight malaise, but even these mild infections eventually produce a state of malnutrition

The **blood picture** usually shows a considerable eosinophilia with an absolute decrease in the other white cell elements, and a slight macrocytic (nutritional) anæmia, unless there has been much blood loss, when the picture may be confused by a microcytic tendency

DIAGNOSIS

The **diagnosis** will usually depend on the finding of the characteristic eggs in the stools although after purgation the adults may be found The eggs are almost identical with those of *Fasciola hepatica*, the sheep fluke that rarely affects man, and with those of *Echinostoma*, of which several species have been reported as parasitizing man occasionally

PREVENTION AND TREATMENT

Consciousness of the mode of infection and a very modest degree of intelligence on the part of the potential victims are the only requirements for prevention Abstinence from eating the incriminated aquatic vegetations is even unnecessary, as, if it is peeled without the aid of the teeth and well washed, infection will be avoided, for the cercariæ do not encyst in the edible portions Immersion in boiling water for a few seconds should however be advocated as a safer procedure In view of the simplicity of this method, discussion on other methods of breaking the cycle such as the destruction of snails and protection of the water courses from contamination, both of which will always be very difficult, would be purely academic The latter would present insuperable difficulties in most endemic areas, as pigs are the main reservoirs of infection

[illegible] carbon tetrachloride, and hexyl
used for other intestinal

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HYDATID DISEASE

pigs,
tape
a per

and other organs producing pathological changes mainly but not entirely by pressure This disease occurs in temperate and cold climates principally where sheep raising is practised extensively, but it is also encountered in a few tropical and subtropical areas

In view of the fact that it is in no sense a tropical disease and that it is usually dealt with adequately in standard textbooks on medicine and surgery, hydatid disease is only discussed summarily here

Geographical distribution —Hydatid disease has an extensive distribution throughout the world, but the most important foci are Iceland central and south eastern Europe, North and South Africa, South Australia, Tasmania, and New Zealand and Uruguay, Argentina and Chile It also occurs extensively in Palestine, Syria, Arabia, and Iraq, and in Siberia

In India the disease is comparatively rare, but perhaps not as rare as published reports would indicate (Editorial 1938) and there are undoubtedly isolated foci where a higher human infection rate exists (Sami 1938)

ÆTIOLOGY

The causal organism —*Echinococcus granulosus* is a minute worm *3 to 6 millimetres in length, consisting of* a scolex, a neck, and one immature one mature and one gravid proglottid It is an intestinal parasite of the dog the wolf the jackal and rarely the domestic cat The principal intermediate hosts are sheep cattle, and pigs, but many other animals act as intermediate hosts notably horses and camels Man is infected sporadically taking the place of an intermediate host in the infection sequence

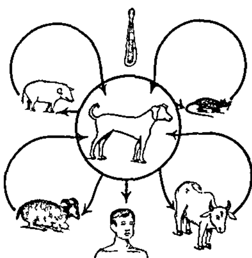


Figure 180 Showing the transmission cycles in hydatid infection

The life cycle —The egg which is indistinguishable from that of the *Tæniæ* is ingested by the sheep or other intermediate host *In the host s stomach* the outer shell is digested off and the o n c h o s p h e r e e m e r g e s in the duodenum where it penetrates the intestinal wall to reach the mesenteric venules It is usually filtered out in the liver but may work its way through these capillaries and even those of the lung to reach the systemic circulation and any organ or tissue of the body Wherever it is held up *it is either destroyed* quickly by the tissue reaction or it develops into a hydatid cyst and commences to grow *Within this cyst brood* capsules containing scolices develop Wh [illegible] or is killed and is devoured by a potential [illegible] them selves to the intestinal mucosa [illegible] coccus When the adult is mature the [illegible] ed, and

the uterus bursts discharging the ova into the bowel lumen to be passed out with the stools, or the detached proglottid itself may pass out of the intestinal canal before discharging the ova Whichever happens, the cycle is now complete and the ova are ready to be ingested by another intermediate host

It will be seen that man plays no part in the natural life cycle of the worm His infection is incidental and the worms that infect him find themselves in a *cul-de-sac*, at least in all civilized countries

EPIDEMIOLOGY

There is evidence that climate *per se* has some influence on the distribution of the disease For example, in Australia conditions are very similar throughout the country, yet it is only in the south that the disease is a serious problem and again it is difficult to explain entirely satisfactorily its relative infrequency in India although here there are undoubtedly other important factors besides the climate

The disease is prevalent only in those countries where man the dog, and sheep (or less commonly cattle and the pig) come into close association, and it occurs mainly amongst those members of the population that associate with dogs, *e g* farmers, shepherds and dog fanciers

Whilst the diagnosis is often delayed until late middle life this is because the hydatid takes many years to reach clinical proportions when it is located in some non-vital structure such as the liver and it is believed that many, or possibly most infections occur during childhood The sexes are affected equally

Factors in the infection of man—From the point of view of man, sheep and other domestic—and possibly also wild—herbivores are the reservoirs of infection and dogs—primarily, and to much less extent other carnivores—are the vectors The two primary factors in the infection of man are

(i) The infection rate amongst dogs

(ii) The number of dogs in a locality (*a*) that may be directly associated with man (*b*) that may contaminate man's water or food and (*c*) that may contaminate sheep and cattle pastures

(iii) The closeness of (*a*) the direct association between dogs and man and the extent of the opportunity for the former to contaminate (*b*) man's food or water and (*c*) sheep or cattle pastures

The secondary factors on which the infection rate in dogs will depend are

(iv) The number of infected sheep or other domestic or wild herbivores in the locality, (in sheep 90 per cent of the hydatids cysts are fertile against 24 per cent of those of other herbivores (Perez Fontana 1936) so that the former are far more important)

(v) The opportunities that dogs enjoy of feeding on the viscera of herbivores

The subject could be discussed briefly under each of these headings

(i) In many countries, the infection rate amongst dogs is very high, up to 50 per cent (South Australia), whereas in others (U.S.A) canine infection is almost unknown (Sawitz, 1938) There is a rough parallelism between canine and human infections but the human infection rate is nearly always on a much lower plain At one time in Iceland where infection rate amongst dogs was 30 per cent, it was stated that nearly 20 per

cent of the population was infected, whereas in countries where infec in dogs is rare, e g the United States and Canada, only 29 autochthon cases have been reported in over a hundred years (Magath, 1941)

For India, only two reports need be quoted, Sami (*loc cit*) found per cent of 89 dogs infected in a rural district in the Punjab where he ported 40 human cases seen in a period of five years, whereas Maplest (1933) found only two infected out of 100 dogs examined in Calc where the human disease is undoubtedly rare

In Iraq, Senekji and Beattie (1940) found 17 8 per cent of 123 d infected

The infection rate in dogs will depend on factors (iv) and (v)

(ii) The disease is generally more common in countries and amon communities in which there is a high proportion of dogs to human bein in Uruguay, Perez Fontana (*loc cit*) reports a ratio of dog man=2 1 houses where hydatid disease occurs, against 1 8 in the general commun

(iii) (*a*) The question of direct association between man and d is a matter of practice, to which it is impossible to attach figures Wh dogs are important as draft animals, as in Iceland and other cold cou tries, or where they are an important part of the farm personnel, as sheepdogs, they are treated almost as human beings and given free acc to the living and sleeping quarters (a modification of this practice h caused a recent reduction in the incidence of the disease in Iceland) many other instances, children are allowed to play freely with dogs B in certain eastern countries, e g amongst the Hindus in India, dogs a looked upon as unclean animals and are allowed to exist as outside sca engers only This is the important factor in determining the high in dence of the disease in the former communities e g Iceland and N Zealand and the comparative rarity in others, e g India

(*b*) The indirect association by contamination of drinking water an food supplies of the population may obviously be a danger in some cou tries, but it has never been given an important place as a cause of t disease

(*c*) The chances of the infection of sheep, cattle and pigs from th promiscuous defecation of dogs in pastures will be a constant danger an will depend mainly on the numbers of uncontrolled dogs that there are any locality, and the propinquity of the pastures to the village, away fro which the dogs seldom stray any distance, except those that are used fo herding cattle

[illegible] is 7 to 10 per cen [illegible] Near East foci th [illegible]ekji & Beattie (*lo* [illegible] per cent in cattl [illegible] On the other hanc In these localities the [illegible] in India the infection rate in sheep and cattle was sometimes also high in Calcutta the writer could always obtain several hydatid livers any da by visiting a slaughter house and in the United States it is far from neg ligible, but for reasons given here the incidence of hydatid disease is no high in either of these countries The infection amongst domestic her bivores is probably maintained by cross infection from wild carnivores an herbivores (Riley, 1933)

(i) In many countries (e g in South America and New Zealand) dogs have in the past been allowed to feed on the livers of slaughtered sheep especially those that were diseased and therefore of no value This practice has declined as a result of propaganda as well as because of the economic fact that liver is now more valuable In the United States, slaughter houses are better controlled, so that the incidence of infection amongst dogs and thence amongst human beings, is low The higher commercial value of entrails in India has also been a factor in keeping the infection rate in dogs at a comparatively low level in most parts of the country In that country the low association index between man and dogs and the climate, already mentioned, are also factors

PATHOLOGY

The pathogenesis is caused by, (i) the pressure of the growing parasite, (ii) the seeping through the capsule of small quantities of allergins and toxins, (iii) the rupture of an hydatid cyst with the sudden release of large quantities of hydatid fluid containing allergins toxins and daughter cysts into the blood stream, a serous cavity, the lung, or a hollow viscus, (iv) the development of secondary cysts in other organs and tissues and (v), as a common complication the infection and suppuration of an hydatid cyst

Distribution of the lesions —When the onchospheres find their way into the portal circulation the first organ that they reach will be the liver, about three-quarters of the hydatid cysts recognized clinically or post mortem occur here, of which four out of five are in the right lobe Some will work their way through the liver, and of these roughly half will be held up in the next set of [illegible]
cent of hydatid cysts are fou [illegible]
the arterial blood and are c [illegible]
other sites, roughly in the ord [illegible]
tissue bone muscle, kidneys [illegible]
The high percentage reported as occurring in the peritoneum are certainly mainly due to metastases from a ruptured primary hydatid

Development of the hydatid cyst —Of the onchospheres that come to rest in the various organs, most probably the majority are destroyed by the tissue reactions those that survive develop into hydatid cysts and grow, reaching a size of 250 microns in about three weeks They are now surrounded by a characteristic tissue reaction, immediately around the cyst are endothelial cells and giant cells, which are surrounded by a layer of fibroblasts with new capillary formations and infiltrating eosinophils, and an outer layer of denser fibrous tissue When a cyst is located in the [illegible] month has
[illegible] n man the
[illegible] attain the
[illegible] zable clin-

As the cyst grows, its outer covering becomes thicker and less permeable so that tissues in which it lies react less specifically but rather as they would to any foreign body The mature cyst consists of three layers, one of host and two of [illegible]

slight tension in which will be found 'hydatid sand', consisting of brood

Exogenous budding also occurs —In such cases the tumour develops a much more 'malignant' character, as it invades rather than compresses the surrounding tissue and eventually a large multiloculated cyst which may involve practically the whole liver will result Also without rupturing it may give rise to metastases (It is a matter of controversy whether this exogenous budding is not the characteristic of a different species or strain of echinococcus The evidence for this is that it commonly occurs only in a few geographical localities, *e g* in Central Europe, but the present consensus is that there is only one species and that some special condition determines its special development)

When the cyst grows within the skull or the spinal column, it naturally

like that of cystic disease of the bone, there is rarefaction of the bone and spontaneous fracture is likely to occur

Spontaneous rupture —This is not an uncommon incident Hydatids of the liver usually rupture into the peritoneum, or into the gall-bladder or bile ducts In the former case, the only immediate result may be shock and allergic manifestations, but after several years a large number of cysts may develop in various parts of the peritoneal cavity In the latter, the daughter cysts may cause a temporary blocking of the common bile duct, but the more serious consequence will be the almost inevitable infection of the cyst cavity

In the lung, rupture into a bronchus is not uncommon If the cyst is a large one, the incident may drown the patient, but, if he survives this, the prognosis is usually good

Suppuration.—This may occur in any cyst, but in the case of a unilocular cyst it is usually the result of a leak or rupture into a hollow viscus The suppuration rate amongst multilocular hydatids is much higher than amongst the unilocular cysts

The changes that occur when hydatid cysts develop in other, rarer locations need not be discussed here

Calcification —When a hydatid cyst dies, the fluid will be absorbed slowly and be partially replaced by caseous matter The cyst wall shrinks and may become calcified What remains of the cyst is now completely surrounded by fibrous tissue, and causing no further symptoms is perhaps discovered *post mortem*

SYMPTOMATOLOGY

Latent period —After infection it will usually be from five to twenty years before the first symptoms appear, and it has been estimated that in about 25 per cent of cases the cyst remains symptomless throughout life

Onset and course —The onset of symptoms may be very gradual, or it may be sudden, either due to the bursting or suppuration of a hydatid cyst It will be appreciated from consideration of the pathology of the condition that the nature of the symptoms in either case will vary accord-

ing to the site of the cyst and in the latter according to the direction in which it bursts

the patient will immediately suffer from shock and possibly an urticrial rash a little later, after which there may be another latent period of five to ten years before the secondary hydatids in the peritoneum begin to cause symptoms Or, if it bursts into a bile duct there may be biliary colic and obstructive jaundice and later suppuration with pyrexia and other complications associated with a liver abscess If it bursts into the pleural cavity, from the liver or from the lung after initial shock the signs will be those of pleurisy with effusion

Multilocular or alveolar hydatids on account of their invasive nature more readily become infected so that irregular pyrexia and pain suggestive of hepatitis or liver abscess will occur without definite rupture

be asphyxiated by the fluid and the daughter cysts obstructing the bronchi or he may be able to cough up the contents in such cases about 75 per cent recover spontaneously but in others a lung abscess may develop

In the **brain**, the pressure symptoms will usually appear earlier but at first they may amount to little more than headache and visual disturbance and the hydatid may reach a considerable size—demonstrable by x ray—before the more serious signs and symptoms of intracranial pressure cause a diagnosis of tumour to be made Again everything will depend on the localization Sudden death may occur from pressure on vital areas or rupture of a cyst into one of the ventricles

In the **bones**, pain will usually be the first symptom later there may be deformity and spontaneous fracture

In the **kidney**, the condition will be suggestive of a hydronephrosis or a tumour Similarly, in other organs and tissues the symptoms will be those of a benign tumour, and when it is palpable of a cystic tumour

DIAGNOSIS

This is a matter of very great importance as even in countries such as Australia and New Zealand where the disease is common only about half the cases reported are diagnosed pre operatively and for proper treatment accurate diagnosis is essential Diagnosis can be considered under six headings —

(i) **Clinical**—The only pathognomonic finding is a "hydatid thrill", [illegible]

with the minimum of general or local effects

(ii)
can be re
Roentgen
or bones
soft tissues

(iii) **Blood picture.**—This will provide little help in countries where helminthic infections are common Eosinophilia will depend on there being some seepage of hydatid fluid through the cyst wall, and a count of from 10 to 20 per cent will be found in most active cases In the case of a rupture occurring in the cyst wall, as a result of ill-advised interference, or otherwise, there will be a sharp rise in the eosinophil count However, a low eosinophil count does not exclude hydatid

(iv) **Serum tests**—Useful information will be obtained from two such tests —

(a) *The precipitin test.*—This is done with fresh carbolised hydatid fluid

datid
tage
per
is in
ains

(v) **Intradermal (Casoni) test**—This is probably the most useful of the immunological tests, it gives the highest percentage of positive results
few false positives
(of proved activ-
with a standard
nade from almost
give 0 01 c cm by
t least one centi

(vi) **Identification of hydatid material**—It is not good practice to tap a cyst through the abdominal wall, as, even if the procedure is followed immediately by open operation, some fluid with contained daughter cysts may escape into the peritoneal cavity, and give rise to metastases How-
with its contained
en a cyst bursts
case, the brood

PREVENTION

The reader should again turn to p 739 where the factors in the infection of man are discussed

The dog is not only the most important definitive host but he is the link between man and any other reservoirs of infection Measures must therefore, be directed towards—

(a) The prevention of infection in dogs by proper control of town and country abattoirs so that dogs do not have access to the entrails of infected animals

(c) The reduction of the direct association between dogs and man this can be done by reducing the number of dogs as above but also by

(i) keeping dogs out of the houses
(ii) not allowing them to lick out plates or other utensils used by man
(iii) avoiding the fondling of dogs and
(iv) forbidding children from playing with dogs

These measures against dogs are particularly applicable in countries where there is a high percentage of infection amongst dogs In other countries, the precautions might be relaxed regarding individual dogs that are known by careful and repeated examination of their stools to be uninfected and that are kept under proper control so that their chances of access to infected material are minimal

Some of these measures can be aided by suitable legislation but **education and propaganda** will be essential to achieve success in the prevention of this infection Already a very considerable degree of success has been achieved in Australia and New Zealand and also in Iceland

TREATMENT

No drug has yet been found that has any specific effect on the parasite in the stages in which it occurs in man It seems very possible that a specific might be found that would destroy the parasite in its early stages but it would be difficult to establish its efficacy and its practical use would be limited to the periodic administration to those under serious risk, however, even in such cases other preventive measures would be preferable The insulation of the cyst by the thick fibrous capsule that occurs in its later stages makes it problematical if a drug will ever be found that will penetrate the cyst and destroy its contents Treatment must therefore be expectant or surgical

Surgical—It will naturally depend on the location of the hydatid whether this is possible or not Hydatids of the liver are those that call for surgical treatment most frequently The aim must be to remove the contents and the parasitic layers of the cyst and to close the cavity as far as possible, without open drainage This must be done without any contamination of the peritoneal cavity with the hydatid fluid

It would be out of place to describe the surgical procedures in detail
cavity
unding
of the
destroy
the daughter cysts and scolices, cutting down on and shelling out the parasitic layers of the cyst, and again swabbing out the cavity with 10 per cent formalin

PROGNOSIS

Hydatid disease is always a serious condition but its seriousness depends very largely on the location of the cyst and when operative treatment is undertaken, on the experience and skill of the surgeon In the hands of a skilled surgeon, the immediate prognosis in unilocular liver hydatids is good, but recurrences in the peritoneum still occur in a considerable percentage of cases The prognosis in multilocular and suppurating hydatids is bad

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NUTRITION AND NUTRITIONAL DISORDERS IN THE TROPICS

NORMAL DIETETIC REQUIREMENTS

Introduction.—For growth and repair of the human frame and for the production of energy, a certain quantity of food is necessary. The three

energy-producing principles of food are protein, fat, and carbohydrate but there are a number of other essential nutrient elements, for example, minerals salts, the most important of which are those of iron, calcium and phosphorus, and the vitamins, water is also essential The food requirements of man have been studied very extensively, although it would be absurd to suggest that there was not a very great deal more to be learned The energy value of different food substances and the energy requirements of the organism can be estimated The unit of expression

usually called, and a gramme of fat will produce nine calories of energy (or heat) Although the calorie value of the mineral salts and vitamins is negligible, they are essential for body-building purposes and for the proper utilization of the energy-producing foods

Calorie Requirements —The calorie requirements of man vary according to the age and size of the individual, as well as the type of work that he or she is doing There are formulæ for calculating calorie requirements dependent on weight and body surface, but for practical purposes it is usual to take a 'basic' calorie allowance, to apply coefficients for individuals of different ages and for special conditions such as pregnancy

TABLE XIX*

Work	Supplementary allowance
Light work	75 calories per hour of work
Moderate work	75 — 150 calories
Hard work	150 — 300 calories
Very hard work	300 calories upwards

Age in years	*Coefficient*	*Calories*
1 — 2	0 35	840
2 — 3	0 42	1000
3 — 5	0 5	1200
5 — 7	0 6	1440
7 — 9	0 7	1680
9 — 11	0 8	1920
11 — 12	0 9	2160
12 — 15†	1 0	2400
Males 15 upwards	1 0	2400
Women not pregnant	0 9	2160
Women pregnant	1 0	2400
Women lactating	1 25	3000

It is not uncommon to apply the coefficient of 0 9 as a maximum to women, except of course pregnant and lactating women For babies under the age of one year, the calorie requirements are best supplied on a body-weight basis, thus —

Under six months	100 calories per kilogramme or 45 calories per pound
Six months but under one year	90 calories per kilogramme or 41 calories per pound

* Recommended by The Technical Commission for the Study of Nutrition of the Health Organization of the League of Nations (1936)
† Meets needs of puberty

An allowance will also have to be made for the muscular activities of children, this is usually calculated as 75 calories per hour of active play

be roughly

Protein Fat Carbohydrate=1 1 5

It is, however, essential for purposes of body building that a diet should include a sufficiency of good protein

The composition of all common foodstuffs in terms of protein, fat and carbohydrate has been worked out and can be read from the many tables that have been prepared, these tables usually give the calorie value of a given weight of the substances but, if they do not, this can easily be calculated from their composition Table XXIV at the end of this chapter, which supplies these data for certain common foodstuffs is given as an example only Workers in tropical countries should always obtain dietary tables for the common foodstuffs of the country in which they are living, in India, for example, from *Health Bulletin No 23* (Aykroyd 1940)

Protein Requirements.—The protein intake of an adult should not be less than 1 gramme per kilogramme (or 0 45 grammes per pound), but the requirements of growing children are proportionately very much greater, the amounts shown in the following table are recommended

TABLE XX

Age in years	*Protein requirements in grammes per kilo of body-weight*
1—3	3.5
3—5	3.0
5—12	2.5
12—15	2.5*
15—17	2.0
17—21	1.5
21 upwards	1.0
Women pregnant 0—3 months	1.0
" 4—9 "	1.5
lactating	2.0

Protein is built up from chemically simpler substances, amino-acids During metabolism these are absorbed and re-arranged as body proteins There are about twenty-two different amino acids some ten of which

children and pregnant or lactating women

Fat Requirements [illegible]
for this dietary elemen[illegible]
considerably with the c[illegible]
is often given as the c[illegible]

* Meets needs of puberty

and 60 grammes Perhaps more important is the nature of the fat, and at least half should be of animal origin A function of fat is its vitamin carrying capacity and fats of animal origin are on the whole a richer source of vitamins, however, perhaps more important, fat dissolves and increases *the absorption of the fat-soluble vitamins* Further, certain unsaturated fatty acids, *e g* linoleic and arachidonic acid, appear to be essential dietary elements

Carbohydrates.—These are the main sources of energy, and except under starvation conditions are more likely to be taken in excessive than in deficient quantities They are the main constituent of cereals and root vegetables, and sugar consists solely of carbohydrates

Mineral Requirements.—*Very small quantities of these are required* but the minimum requirements have been calculated:—

Calcium:—Fish, milk, eggs and vegetables are rich in calcium Cereals, especially rice, are poor sources, whole meal is, however, a moderately good source

The daily requirement of an adult is about 0 7 grammes, but that of a child, who needs an excess of calcium for bone formation, is at least *1 0 gramme, of a pregnant woman 1 5 grammes, and of a lactating* woman 2 0 grammes

Phosphorus.—This is seldom deficient in any diet adequate in calories and other essentials It occurs in most food substances and cereals are a rich source of phosphorus, some will be lost in washing and cooking

Iron—This occurs in many foods, in cereals, pulses (legumes), fruit, vegetables, and meat, especially liver, but it is present in negligible quantity *in milk. Iron is not however assimilated from the food quantitatively,* in some foods most of the iron is 'available', that is to say, easily assimi-
older
liable
food
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s It
loss,
, *e g*
hookworm infection and hæmorrhoids, that there may be a *relative* iron deficiency, even in persons on a good diet The infant is born with about

The daily iron requirements of the adult have been placed at 12 milligrammes, but in criticizing a diet one should expect at least 20 milligrammes to allow for some of the iron not being 'available' A far better indication of iron deficiency in a population will be obtained by blood
by a diet survey A hypo-
opulation in which there is
r schistosomes will almost
ich an anæmia, even in the
will suggest that the iron
intake is low, and *relatively* inadequate

It will seldom be worth modifying the diet to any extent on account of iron deficiency, it will nearly always be more economical to give additional iron medicinally

Fluorine —This is an essential dietary element Its absence during the period of formation of the teeth appears to lead to early dental caries, and there is some evidence that fluorine present in sufficient quantities (1 part per million) in the drinking water taken in later life will protect the teeth The requirements have been placed at 0.5 milligrammes *per diem*

On the other hand, excess of fluorine in the water will lead not only to band formations and mottling of the enamel of the teeth but to changes in the bones, for example the development of exostoses that may result in the ankylosis of the joints, of the spinal cord, or of the thoracic cage, and eventually to the death of the patient from secondary infection Amounts [illegible]

Copper, iodine, manganese and other minerals —Iodine will only be deficient in certain countries or parts of countries where iodine is absent from the water In such countries special arrangements have to be made for supplying iodine medicinally at intervals throughout the year or in some domestic food ingredient such as salt, in order to prevent goitre

Of the other minerals, there is always sufficient in almost any diet to supply the minimum requirements

The Vitamins —Important as they are, the vitamins have received far more attention than their relative importance warrants on account of the wide advertising of vitamin preparations to both the medical profession and the laity during the last decade It is not very often that a [illegible]

special circumstances such as war
not obtainable

Medical attention was first drawn to the vitamins by certain clinical syndromes that were traced to the gross deficiency of specific vitamins (*e g* beri beri, due to deficiency of vitamin B_1 scurvy, due to deficiency of vitamin C, and rickets, due to the deficiency of vitamin D) Far more important however are the widespread minor degrees of ill health that are attributable to lesser degrees of deficiency

In the determination of pathological processes associated with vitamin deficiencies, it is obvious that there are other factors than the actual amount of the vitamin in the diet or even than the amount absorbed, amongst a group of persons on more-or less the same diet deficient in a particular [illegible]
particular
while yet
factors, so
Amongst these factors are, (a) other dietary substances taken (*e g* large amounts of any vitamin-free cereal appear to increase the requirements

TABLE XXI

Summarized Data on Important Vitamins

Vitamin	Names	Solubility	Sources	Stability	Physiological action	Average adult daily requirements: International units	Average adult daily requirements: milligrammes	Pathological effect of deficiency
A	Anti-infective Carotene provitamin	Fat-soluble	Green vegetables carrots butter liver some fruit eggs and red palm oil	Prolonged heating destroys	Essential for cell growth and replacement especially affects epithelial tissues Precursor of visual purple	5000	3 00	Bitot's spots xerosis and xerophthalmia keratomalacia night blindness phrynoderma or follicular hyperkeratosis dentine defects
B complex: B_1	Thiamin Aneurin	Water-soluble	Yeast unmilled cereals nuts and vegetables some fruits glandular organs meat (Milk is poor source and milled cereals very poor)	Heat-labile with stands 1 0°C acid sol	Controls carbohydrate metabolism by carboxylation of pyruvic acid	330 to 660	1 2	Beri-beri polyneuritis anorexia, cardiac dilatation
B complex: B_2 Complex	Riboflavin	Water soluble	Pulses milk products liver eggs meat some green vegetables and tubers yeast Autolysed yeast (Marmite)	Heat-stable	Factor in enzyme system that regulates cell oxygenation and affects protein and carbohydrate metabolism		2 to 3	Ariboflavinosis or cheilosis glossitis and eye affections dermatitis
B complex: B_2 Complex	Nicotinic acid Niacin	Water soluble	Meat liver yeast whole cereals potatoes carrots pulses (Milk is poor eggs a negligible source)	Heat-stable	Same as Riboflavin and may also affect water and iron metabolism		20	Pellagra or dermatitis glossitis gastro-intestinal and mental disturbances
C	Ascorbic acid	Water soluble	Citrus and other fruits hips and berries *amla* green vegetables tomatoes potatoes. (Little in human milk less in cows)	Heat-labile in presence of oxygen	Formation of collagen and intra-cellular cement substances detoxication	1000 to 2000	50–100 Adults 1 2 Child 3–8 Pregnancy 5–10 per kilo	Scurvy Barlow's disease
D	Calciferol	Fat-soluble	Fish liver oils fish, eggs milk and butter of pasture-fed cattle Action of sunlight on subcutaneous fat	Heat-stable	Balances calcium and phosphorus absorption and execution bone formation	400 to 800		Rickets osteomalacia and osteoporosis failure of calcification
E	α tocopherol	Fat-soluble	Seed germ oils *e g* wheat and rice germ lettuce alfalfa	Heat stable in absence of oxygen	Directs activities of cell nuclei affects cell differentiation and division		6	Habitual abortion muscular dystrophies
K	Pro-thrombin factor	Fat-soluble	Alfalfa spinach cabbage kale cauliflower soya-bean oil pig liver milk and eggs (a little) Intestinal and putrefactive micro-organisms	Heat-stable	Pro-thrombin formation		1 to 10	Hæmorrhage of the new born Hæmorrhagic diatheses in obstructive jaundice and liver disease

of vitamin B_1) (b) infections (*e g* wound sepsis, which similarly appears to increase the requirements of vitamin C), (c) endocrine deficiencies (*vide infra*, myxœdema and pellagra), and (d) the personal factor (an expression that is a cloak for our ignorance) Again, vitamin deficiencies are seldom single, for, if a diet is deficient in one vitamin, it will usually be deficient in one or more other vitamins, especially in those found in the same food stuffs Examples of grouped deficiencies are the fat-soluble vitamins A and D, and the water-soluble B vitamins respectively

[illegible]

to be found in large and small amounts and what diseases and minor disabilities their deficiency causes but in many instances we know their chemical formulæ and the exact daily minimum requirements of the human organism The writer does not propose to discuss the various vitamins in any detail here but only the special dietetic problems that are likely to face the worker in the tropics The reader who is not familiar with this important subject is advised to refer to one of the many standard textbooks on dietetics, but in order to help him to follow the subsequent discussion on the dietary deficiences encountered in the tropics a table giving summarized data on the important vitamins is appended (*see* Table XXI)

DIETETIC REQUIREMENTS IN THE TROPICS

The basic dietary requirements in the tropics are naturally very much the same as they are in temperate climates at least qualitatively but it has been found that quantitatively certain reductions should be made Aykroyd (1941) considers that the calorie requirements of the average male adult Indian for example engaged in a sedentary occupation is 2 160 calories or 10 per cent less than that of the average native of temperate western countries to this he adds 450 calories for the light to moderate work in which the average agriculturist is engaged making a total 2 600 in round figures To this figure he applies the following coefficients —

TABLE XXII

	Co-efficient	*Calories required* (to nearest 100)
Adult male (over 14)	1 0	2 600
Adult female (over 14)	0 8	2 100
Child 12 and 13 years	0 8	2 100
Child 10 and 11 years	0 7	1 800
Child 8 and 9 years	0 6	1 600
Child 6 and 7 years	0 5	1 300
Child 4 and 5 years	0 4	1 000

For pregnant women he allows 2 400 calories and for lactating women 3 000 For those engaged in heavy manual work a further allowance must be made *on the lines of the allowances made for hard work in temperate* countries (*quod vide*)

Protein —Vegetable proteins are as a rule poorer than animal proteins [illegible] natives of the tropics are [illegible] on religious or economic [illegible] protein in their diets As [illegible] at least one fifth of the protein should be of animal origin and for growing children and pregnant and lactating women the proportion should be higher It will be seen from the table of biological values of

protein that, even if meat is taboo, milk and eggs can be taken to provide protein of high biological value

Fat.—The fat requirements are certainly less than in temperate climates A diet containing 50 grammes of fat need scarcely be considered

[illegible]

guineensis) oil which is rich in vitamin A, this palm grows in Malaya Burma, and West Africa, whence some is exported to other tropical countries, *but little of this oil is consumed in India or China Other vegetarian foods that are rich in vitamin A are nuts and soya beans*

Mineral salts and vitamins—There is no satisfactory evidence, except possibly in the cases of vitamin B_1 and choline, that the requirements of these is in any way different from those in temperate climates However, the blood depredations of parasitic infections, more common in the tropics than elsewhere, make the average iron requirements greater than in the *temperate zones, and, conversely, the oral vitamin-D requirements are*

[illegible]

Some tropical dietaries—Data from several tropical countries are available, but India, with its four hundred million inhabitants and its *varied climatic conditions and racial types, provides* a sufficiently wide variety of diets to form the basis of a discussion on tropical dietaries India has possessed an efficient nutritional research unit for about twenty years This was started by Sir Robert McCarrison under the auspices of Indian Research Fund Association and for the last 8 years has been ably dire [illegible]
Coonoor [illegible]
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It has been found that the diet of the poor rice eater is much the same all over India [illegible] quantities of pulses [illegible] ounces daily non [illegible] Con sumption [illegible] ot even this amou [illegible] hile the consumption of milk is usually negligible [illegible] he diet [illegible]

[illegible]

described above

In about 30 per cent of the surveys which were carried out in widely separated areas the average calorie intake was below 2300 per consumption unit [illegible] below any reasonable standard of requirements Again within certain groups some 30 to 40 per cent of families were not obtaining enough food While it is not justifiable to apply these results to India as a whole there can be no doubt that a high percentage of the population is habitually underfed and the extent of undernutrition is of fundamental importance Enough food takes precedence over the right kind of food and to produce more food must be the foremost aim of agricultural policy

Intake of total protein is usually sufficient when the calorie yield of the

TABLE XXIII

Some Indian Diets

(Ounces per consumption unit per day)*

Food	1	2	3	4	5	6
	Assam Tea plantation labourers	Madras Beriberi area Villagers.	Orissa Villagers	Bihar Well-paid industrial families.	Central Provinces. Villagers.	Punjab Villagers.
Rice	19.0 (home-pounded and milled parboiled)	21.9 (mostly milled raw)	24.6 (home-pounded parboiled)	21.0 (milled parboiled)	1.5	none
Wheat	none	none	none	none	none	17.4
Millets	none	none	none	none	16.0†	none
Pulses	1.0	0.8	0.9	3.4	2.0	1.9
Leafy vegetables	0.2	0.4	0.3	0.1	none	4.6 (leafy and non-leafy)
Non-leafy vegetables	3.4	2.9	7.7	6.2	4.5	
Fruit	none	0.2	none	0.9	none	2.5
Vegetable oils	0.3	1.2	0.1	1.8 (mostly ghee) (oils and ghee)	0.3	negligible
Ghee	none	negligible	none		none	1.2
Milk and buttermilk	0.5	1.0–2.0	none	5.7	1.8	8.7
Meat, fish and eggs	0.2	0.1	1.1	1.0	0.1	none
Sugar and jaggery	negligible	0.1	none	0.8	negligible	not reported

1 Wilson and Mitra, (1938)
2 Nutrition Research Laboratories (unpublished)
3. Narindra Singh, (1939)
4 Mitra, K. (1940)
5 Nutrition Research Laboratories (unpublished)
6 Ahmad and Gore (1933)

* A consumption unit is the allowance for one male adult any additional male adult members are counted as one unit, and other members according to the coefficients shown in Table XXIII above

The populations of which the average diets are shown in the above table are normal populations, none of these surveys was taken in a famine area, nor was any particularly poor population, of which there are many in India, included In his invaluable *Health Bulletin No 23*, Dr Aykroyd (1941) gives an example of the type of poor and ill balanced diets that is often encountered in India, this is shown diagrammatically in figure 190 in which a balanced diet suitable for an Indian peasant of a rice growing district is also shown An analysis of these two diets is given in the table below

TABLE XXIV

Summary of an ill-balanced and a well-balanced diet

Constituent	*Amount in ill-balanced diet*	*Amount in well-balanced diet*
Protein in grammes	33	73
Fat	19	74
Carbohydrate "	357	408
Calories "	1750	2590
Calcium "	0.16	1.02
Phosphorus "	0.60	1.47
Iron in milligrammes	9.00	44.00
Vitamin A international units	500	7000
" B_1 " "	160	400
" C, in milligrammes	15	17

protein that even if meat is taboo milk and eggs can be taken to provide protein of high biological value

Fat—The fat requirements are certainly less than in temperate climates A diet containing 50 grammes of fat need scarcely be considered deficient in fat and one containing the classical 100 grammes will usually be too rich for either the native or the

ever it is imp

because some

very poor in vitamin A An exception to this rule is red palm (*Elæis guineensis*) oil which is rich in vitamin A, this palm grows in Malaya Burma and West Africa whence some is exported to other tropical countries but little of this oil is consumed in India or China Other vegetarian foods that are rich in vitamin A are nuts and soya beans

Mineral salts and vitamins—There is no satisfactory evidence except possibly in the cases of vitamin B_1 and choline that the requirements of these is in any way different from those in temperate climates However the blood depredations of parasitic infections more common in the tropics than elsewhere make the average iron requirements greater than in the temperate zones and conversely the oral vitamin D requirements are usually less on account of the longer periods of sunlight to which people are subjected in the tropics (*see* p 764) Iron cooking vessels are often used in the tropics and this probably helps to meet the demand for iron

Some tropical dietaries—Data from several tropical countries are available but India with its four hundred million inhabitants and its varied climatic conditions and racial types provides a sufficiently wide variety of diets to form the basis of a discussion on tropical dietaries India has possessed an efficient nutritional research unit for about twenty years This was started by Sir Robert McCarrison under the auspices of Indian Research Fund Association and for the last 8 years has been ably directed by Dr W R Aykroyd who in his nutrition laboratories at Coonoor and elsewhere has carried out a systematic investigation of Indian dietetics as well as much research work arising therefrom and has in many aspects of a lead to other tropical countries The Indian dietaries is taken from a paper by

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Rice	19 0 (home-pounded and milled parboiled)	21 9 (mostly milled raw)	24 6 (home-pounded parboiled)	21 0 (milled parboiled)	1.5	none
Wheat	none	none	none	none	none	17 4
Millets	none	none	none	none	16 0†	none
Pulses	1 0	0 8	0 9	3 4	2 0	1 9
Leafy vegetables	0 2	0 4	0 3	0 1	none	4 6 (leafy and non-leafy together)
Non leafy vegetables	3 4	2 9	7 7	6 2	4 5	
Fruit	none	0 2	none	0 9	none	2.5
Vegetable oils	0 3	1 2	0 1	1 8 (vegetable oils and ghee together; mostly ghee)	0 3	negligible
Ghee	none	negligible	none		none	1 2
Milk and buttermilk	0 5	1 0–2 0	none	5 7	1 8	8 7
Meat fish and eggs	0 2	0 1	1 1	1 0	0 1	none
Sugar and jaggery	negligible	0 1	none	0 8	negligible	not reported

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Constituent	*Amount in ill-balanced diet*	*Amount in well-balanced diet*
Protein in grammes	38	73
Fat	19	74
Carbohydrate "	357	408
Calories	1750	2590
Calcium "	0 16	1.02
Phosphorus	0 60	1 47
Iron in milligrammes	9 00	44 00
Vitamin A international units	500	7000
B	160	400
C in milligrammes	15	17

It will be seen that the poor and ill-balanced diet is not only deficient in calorie value, but in almost every item of the protective foods Three (1, 2 & 5) out of the six average diets in Table XXIII also are below the minimum requirement in calories, and four (1, 2, 3 & 5) are each defective in several important protective elements

To summarize, it can be said that 30 to 50 per cent of the indigenous inhabitants of India do not eat enough food, and that the diets of the great majority are deficient in several important elements The diet of the rice-eater is usually deficient in iron, and, under conditions of unusual heat,

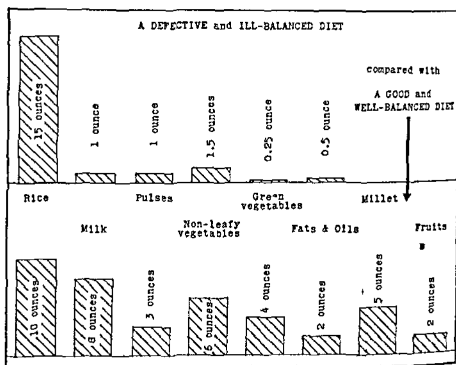


Figure 190

chlorides will also be relatively deficient Many diets are deficient in fat-soluble vitamin A, and in vitamin B_2-complex unless the people take some form of 'country'* beer Vitamin B_1 is deficient usually only in the *diets* ... deficient De-

south

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en are

These remarks can probably be applied to the native inhabitants of most other tropical countries, and certainly to those whose staple diet *is* rice, maize, or some poorer food substance such as tapioca

Rice.—As rice is the staple food of about half the inhabitants of the globe, it is entitled to a few lines of special discussion There are *of course*

* 'Country' beers are crude alcoholic beverages made by fermenting various grains, unlike ordinary beer they are sometimes rich in vitamin B complex

some scores if not hundreds of varieties of rice plant, but it will not be e The gross nature of mical composition is so that can be applied for

When threshed from the head, the grain consists of an outer inedible husk and an inner edible grain The latter consists of an endosperm, with its thin outer layer of aleurone cells, the surrounding pericarp, and the 'germ' The bulk of the endosperm consists of carbohydrate, the aleurone layer contains most of the protein and fat, and the vitamin B_1 is mainly in the germ

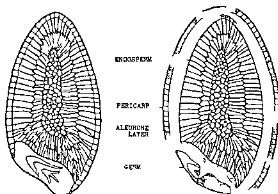


Figure 191 Section of a rice grain showing the effect of milling

There are several ways of preparing the grain for eating, and the composition of the final product depends largely on the way it is prepared The primitive method, a method that is still followed by the large majority of peasants who grow their own rice, is pounding the grain with a heavy wooden pestle in a large wooden or stone mortar This removes the husk, some of the pericarp and ... most of the germ The

loss of protein, fat iron, and vitamin B_1 There are different degrees of milling and the extreme degree of milling is carried out by rubbing the rice between two leather surfaces, this removes the last traces of the aleuron layer and pericarp and leaves a polished pearly-white grain Rice thus treated

A procedure that has been practised mainly in India and is now spreading to other countries is known as parboiling (part boiling) The rice still in the husk is first soaked in water, then steamed for some time, dried and finally husked by one of the methods mentioned above Parboiling has the practical advantage that it makes newly-harvested rice more digestible and facilitates husking, but its real value from the nutrition point of view is that both the iron and vitamin B_1, and to some extent other B vitamins also, in the germ are dissolved and much of these are absorbed by the endosperm, therefore, much less of the iron and vitamins are lost during subsequent husking

The following table shows the effects of milling and parboiling on the composition of rice

TABLE XXV

Comparison of Raw Rice and Parboiled Rice

	Raw rice		*Parboiled rice*	
	Milled	*Home pounded*	*Milled*	*Home pounded*
Protein, per cent	6 9	8.5	6 4	8.5
Fat, "	0 4	0 6	0 4	0 6
Calcium "	0 01	0 01	0 01	0 01
Phosphorus "	0 11	0 17	0 15	0.23
Iron mg "	1.00	2.80	2.20	2.80
B_1 I U per 100 g	20	60	70	90
Digestibility	+++	+	+++	++
Storing properties	good	poor	poor	very poor

There is further considerable loss, up to 50 per cent, of important ingredients during washing and cooking, especially if the cooking water *is discarded, which of course it should not be*

It will thus be obvious that the practice of machine milling is a bad one from a nutritional point of view One might ask 'Why then is it practised and why is it difficult to eradicate the practice?' There are several reasons *for this, some of which are sound, others are not Firstly, (a)* the industrial worker finds it very convenient to buy rice ready for cooking instead of pounding it himself This saving of trouble will often appeal to the villager also and he frequently takes his rice to be milled, this is done almost free of cost, because the miller makes his profit out of the 'polishings' *(b)* When rice has to be conveyed some distance, *freight* [illegible] ould be [illegible] urther, [illegible] husked rice keeps well if it is stored in a dry and well-ventilated place, as the husk protects it, but, when the husk is removed, the fat in the aleurone layer is exposed to attack by micro-organisms and become rancid very quickly *Parboiled rice, even if subsequently milled, does not keep as well as raw* milled rice Finally, (e) æsthetically a plate of spotless white rice is much more appealing than one of flecked and discoloured, home-pounded rice Thus, it will be seen that the problem is not altogether a simple one, but the dangers to health in allowing persons who eat little else but rice to use polished rice are so great that *it is essential that these difficulties should* somehow be overcome

One method is to limit the degree of milling to which rice may be subjected Another would be to improve the mechanical methods of husking rice Experiments have been carried out with a wooden grinder and it has been shown that, by using this, three times as much fat and vitamin B_1 are preserved as when the same sample is subjected to machine milling

The introduction of legislative measures to prohibit machine-milling is likely to be resisted on account of vested interests Further, in a locality where the milling has been practised for many years and the people have acquired the habit of buying milled rice in small quantities as they require it, it would be impracticable *suddenly to prohibit the milling of rice*

THE EFFECTS OE DEFICIENT DIET ON HEALTH

General Effects —It may be taken as axiomatic that the physique of a nation is dependent to a large extent on its food Numerous examples of peoples of the same racial type living under comparable climatic condi-

tions in which those taking a better diet are physically far superior could [illegible]

physically much finer types than the rice-eating southern Indian It is however harder to appraise the effect of diet on health, as distinct from physique, that is, on morbidity and mortality, as so many other factors come into operation In India, at least a third of the population is quantitatively underfed and an even greater proportion lives on a qualitatively defective diet (*vide supra*), and the health of the country is admittedly [illegible]

be connected, but how much of this ill-health can be attributed to malnutrition and how much to other factors? The modern sanitarian believes that nutrition is a matter of primary importance Sir Alexander Russell, then public health commissioner with the government of India, in his report for 1935 wrote —

> 'No preventive campaign against malaria against tuberculosis or against leprosy no maternity relief or child welfare activities are likely to achieve any [illegible]

But it is not easy to provide proof from public health returns

Similarly, the clinician cannot fail to believe the importance of diet when he sees the various major and minor defects melting away as his patients are put on to good hospital diet, and their persistence if the same patients are treated in their own homes But he again finds it difficult to show any proof that these same people would not have suffered the various infections, malaria, amœbiasis, kala azar, typhoid, or ancylostomiasis, that probably brought them in to hospital, whatever their diet had been While there is little indication that the incidence or the course of the disease in the cases of smallpox, plague, kala-azar, sleeping sickness, or yellow fever are affected by the patient s state of nutrition, cholera, [illegible]

malnutrition, but recently this doctrine has been questioned and some of [illegible]

except in the ill-nourished About the association of tuberculosis and malnutrition there is little doubt The standard example is Germany in the last war, here the incidence rose rapidly, almost certainly as a result of the widespread malnutrition from which the whole population suffered Finally, though it seems doubtful if malnutrition could determine specific dysentery infections, there are certainly many non-specific 'intestinal fluxes' that are caused by defective dietary (*vide supra*)

Some relevant data can be obtained from famine reports In India Nicol (1940), reporting on the Hissar famine of 1938 and 1939, showed that there w
that di
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75 per
per cen
stand though one would certainly expect an increase in mortality The total number of deaths in 1939 was 37,767 as compared with 20,910 in 1937 The increase in the death rate was most marked in the under-ten-years age group, and of the total deaths in 1939, 21,160 were in this age group, that is 56 per cent of all deaths in Hissar were in children under 10 years of age This is in keeping with the well-established fact that the effects of malnutrition are most noticeable in infants and young children Forty nine per cent of all deaths in British India were in children under 10 years of age, if these figures are compared with that for Hissar (56 per cent) and England and Wales (12 per cent), it will be seen that the figure for British India as a whole is much nearer to that of the famine area than to that of England and Wales The deduction is obvious

The *recorded* infantile mortality in British India in 1939 was 155 per 1000 live births, the *actual* infantile mortality probably being much greater Another special group in which the death rate is very high is amongst pregnant and parturient women Maternal mortality has been variously estimated in different large areas in India as from 16 to 25 per mille, and in one investigation in Assam an average figure of 42 was given, with for one group the extraordinary figure of 137 per 1000 births (Balfour 1927), this has to be compared with 2 82 for England and Wales in 1939 Neal Edwards (1940) found that 23 3 per cent of the maternal deaths in Calcutta were due to anæmia, whereas anæmia was also a contributory cause in many more cases and Napier and Neal Edwards (1941) considered that the main cause of this anæmia was dietetic

All this points to the fact that malnutrition is an important factor in the production of ill-health and high mortality in India For other tropical countries, *e g* for Java by de Haas (1939 & 1940), similar figures have been produced, and the writer believes that it is fair to assume that much of the ill health in the tropics is due to malnutrition amongst the native inhabitants

Special effects of dietary deficiencies —Starvation A person who for any length of time eats less than the amount that may be considered his minimum requirements is being starved The result of starvation is the loss of body fat, first the adve
abdominal wall and the fat in
in other parts of the body T
muscle followed by the unstrip
and eventually the heart In
be looked upon as a natural reserve, has been used up, the subject
lethargic and all muscular effort is reduced to a minimum, after which

there is a slowing down of metabolism, evidenced by a fall of pulse and respiration rate, until a point of compromise is reached, probably in an adult at about one thousand calories daily intake (it will be relatively higher in a child who requires some food for body-building purposes) If the intake falls below this, vital organs will be affected and the subject will eventually die In complete starvation specific deficiencies do not usually develop, but in partial starvation, these may complicate the picture and hurry the end, scurvy (vitamin-C deficiency) is a common disease during famines

Protein deficiency.—This may be (*a*) an absolute deficiency as in starvation, (*b*) a relative deficiency as in pregnant and lactating women and growing children whose protein requirements are relatively far greater than those of adult men, (*c*) due to the unsuitability of the protein, *e g* zein of maize, or (*d*) due to the defective powers of assimilation of the individual

This is the specific deficiency most commonly associated with starvation and œdema which is one of the earliest manifestations is often referred to as 'famine dropsy , the condition is likely to occur when the protein intake falls below 30 grammes daily There is hypoprotinæmia, the deficiency is mainly in the serum albumin fraction The œdema is usually confined to the legs, but the whole body may be involved There is also polyuria and some anæmia but most of the other symptoms that may be associated can probably be attributed to the general starvation There is of course no ætiological association between famine dropsy or 'war œdema' as it is sometimes called and epidemic dropsy (*vide infra*)

Hypoproteinæmia may occur in late pregnancy and is sometimes associated with anæmia, it occurs in women on a diet which is low in protein and although well above the 30 gramme level, is insufficient to meet the additional demands

Vitamin-A deficiency—This would appear to be one of the most common defects in tropical diets, partly on account of the low fat intake, and it is surprising that there are not more definite clinical defects attributable to this deficiency Vitamin A was at one time known as the anti-

ness xerophthalmia, phrynoderma and possibly certain types of stone in the kidney Some of the eye conditions hitherto attributed to vitamin A deficiency have recently been shown to respond better to riboflavin than to vitamin A administration, it seems possible that the action is synergistic and that both should be given

Night-blindness—The association of night blindness and vitamin-A deficiency is so well established that light adaptation tests with an apparatus known as a biophotometer are employed as one of the standard methods of testing for vitamin-A deficiency Inability to see at all in a dim light is a common defect in poor populations in the tropics the condition is often associated with other vitamin-A deficiencies and with anæmia-produc-
ing d ... fact leads the writer
in certain types of
Bright sunlight
46)

Xerophthalmia —This condition of dryness of the conjunctiva is indicated in its earliest stages by the appearance of Bitot's spots white exuda

Phrynoderma —Nicholls (1933) in Ceylon Loewenthal (1933) in East Africa and Frazier and Hu (1934) in China *reported a follicular hyper* keratosis particularly on the exten
they associated with *vitamin A def*
name phrynoderma on account of
skin which is a very apt compa
amongst children in several parts of India

Renal calculi —McCarrison produced renal calculi in rats by feeding *them on a diet deficient* in vitamin A and has suggested that the urinary lithiasis that is common in some parts of India might be due to vitamin A deficiency

Prevention and treatment —*All these conditions can be prevented by increasing the intake of articles rich in* vitamin A, these are leafy vegetables (*e g* spinach cabbage celery, amaranth leaves and coriander leaves) carrots fruits (particularly mango and papaya) liver eggs and butter Vegetable oils contain no vitamin A with the exception of red palm oil which contains large amounts of pro vitamin A or carotene which is converted into vitamin A in the body

Medic is halibut liver oil as this contains very drop contains several thousand units (IU) is vitamin but has to be taken in slightly larger doses a drachm and a half will provide an adequate daily dose of vitamin A The latter oil, although not so rich in vitamin A *contains large amounts of vitamin D and has other nutritional* qualities which make it preferable During the war the cod liver oil has been difficult to obtain and several substitutes have been tried shark liver oil *has* prove mmercial concentrates are also available vitamin A probably do not exceed 5 000 be the aim in treatment and even then response may be slow

Vitamin B deficiency —*This vitamin has recently become a popular* panacea and is at present grossly abused by the over enthusiastic but it does certainly appear to have a beneficial effect in a large variety of conditions *e g* in the polyneuritis of alcoholism pregnancy and senility and also in *certain neurites of doubtful origin in cardiac failure of obscure* origin with hypertrophy in oedema and in anorexia and functional disorders of the intestinal tract due to lack of tone As the diets of rice eating people are very liable to be deficient in this vitamin it is probable that many of the conditions of the nature of those mentioned above from which they may suffer can *to some extent be attributed to vitamin B, deficiency* but the only definite syndrome associated with this deficiency is beri beri this disease will be discussed separately *The prevention and treatment* of this deficiency will be discussed under BERI BERI

Vitamin B complex deficiency —This is a common deficiency in the tropics *Many fractions* of this vitamin have been identified The quantitative occurrence of each fraction has not been so thoroughly worked out as in the case of other vitamins but *as a general rule* liver brewer s yeast certain green vegetables pulses meat fish and poultry are the richest

sources Vitamin B_2 complex occurs in large amounts in dried brewer s or in autolysed yeast and these are the best medicinal sources It will be best to consider the effects of these different fractions separately

Nicotinic acid or **niacin,** deficiency is an important even if not the main factor in the ætiology of pellagra (*vide infra*) it also plays some part in the production of non specific gastro intestinal disturbances *e g* sprue (*quod vide*) and toxic psychoses and encephalopathy As our experience widens it will probably be found that there are many other minor health defects especially skin conditions commonly encountered in the tropics which can be attributed to niacin deficiency

Riboflavin —Evidence of the deficiency of this fraction is much more frequently encountered than that of niacin the main clinical evidence of ariboflavinosis is glossitis cheilosis angular stomatitis and certain eye changes namely congestion of the sclera vascularization and later ulceration of the cornea and blepharospasm associated with photophobia visual fatigue dimness of vision a burning sensation and a feeling of roughness of the eyelids

There is superficial denudation and redness at the line of closure of the lips maceration fissuring and a yellowish crust formation at the angles of the mouth seborrhœic dermatitis around the alæ nasi and just inside the nose at the canthi of the eyes and on the ears and deep magenta coloration and fissuring of the tongue and swelling and flattening of the papillæ or the tongue may show oval or irregular areas of desquamation with atrophic centres and raised pinkish edges These mouth changes are associated with soreness and burning of the tongue and lips and dysphagia The subjective eye symptoms often precede the glossitis and angular stomatitis but it may be necessary to ask leading questions to elicit

atment There is immediate

n 5 to 15 milligrammes with

definite but it takes several

days to become fully established

The position of **pyridoxin** (vitamin B_6) in human metabolism is not yet fully understood but certain nervous symptoms including irritability insomnia and muscular weakness rigidity and painful spasms and cheilosis in pellagra patients myasthenia and muscular dystrophies chilblains and certain forms of anæmia have improved on the administration of pyridoxin in doses of 10 to 50 milligrammes In rats at least this vitamin appears to play some part in the metabolism of unsaturated fatty acids and it is suggested that its action may be similar in man and that its deficiency is one of the causes of sprue

There are several other fractions included in the vitamin B complex some of which have been identified *e g* pantothenic acid but the only other common tropical syndrome associated with deficiency of vitamin B complex is **tropical macrocytic anæmia,** the evidence that this is associated with vitamin B_2 deficiency is dependent on epidemiological data and on the therapeutic test that is to say the response to the administration of autolysed yeast extracts (marmite or vegex) and other substance rich in this vitamin It has been shown that the isolated vitamins thiamin (B_1) niacin, riboflavin pantothenic acid and pyridoxin (B_6) have no effect on this condition

Tropical macrocytic anæmia occurs in men and women living on a poor diet in the latter it is often associated with pregnancy and in both

sexes with chronic malaria Although there is little doubt that deficiency absolute or relative, of some fraction min-B complex is an important ætiolog nutritional deficiencies, e g protein or and other factors The writer has sug toxicity

Vitamin-C deficiency—Scurvy (*vide infra*) and sub scurvy degrees of vitamin-C deficiency are common in tropical countries particularly amongst labour forces working away from their home surroundings and familiar fruits and vegetables, and during times of famine

Scurvy is the only definite d in many tropical conditions, e g ment is delayed unless sufficient

The prevention and treatment of this deficiency will be discussed under the heading of SCURVY

Vitamin-D deficiency—Despite the fact that many tropical dietaries are deficient in vitamin D, only under very special circumstances does frank rickets occur in the tropics, as the hours of sunshine are many and the majority of people spend much of their time in the open air However minor degrees of rickets do occur amongst the children of both natives of the orthodox classes who do not allow their children sufficient freedom and of sojourners who are too assiduous in protecting their children from the sun

There is an adult form of rickets which is common in northern Indian towns in particular, but which also occurs in other countries amongst women who are kept in *purdah* especially when their diet is deficient in *calcium* This *condition known as osteomalacia* is usually first noticed when the woman is pregnant and her calcium is further depleted by the inexorable demands of the fœtus There is softening and bending of the bones particularly those of the pelvis so that parturition becomes difficult or even impossible The first symptoms are general weakness and girdle pains there may also be tetany The condition usually becomes worse with each succeeding pregnancy, if the woman survives the earlier pregnancies and no preventive measures are taken

The first **preventive** measure is education and the alteration of un hygienic social habits Otherwise it consists in seeing that all pregnant women get a sufficiency of food rich in vitamin D, calcium and phosphorus and a regular period of exposure to sunlight **Treatment,** by appropriate feeding and the giving of vitamin concentrates will only be effective if it is given in the early stages before the bone deformities have become established vitamin D occurs in milk and butter (from pasture fed cattle) liver, and fish-liver oil The last named are the richest source Cod liver oil or shark-liver oil and the pure vitamin 'calciferol', or some proprietary preparation of irradiated ergosterol (*e g* viosterol) are the forms in which it is usually given

ins for ex
the tropics
portions and
the high neonatal death rate, but the subject has not yet been sufficiently studied to make any discussion on it appropriate here

The reader should perhaps here be reminded that few deficiencies are single, and when one deficiency condition is known to exist others should be expected and be looked for

THE PREVENTION OF NUTRITIONAL DEFICIENCIES IN TROPICAL COUNTRIES

Causes of malnutrition.—Before attempting to devise general measures of prevention, it is necessary to enquire what are the causes There is naturally no single formula that will cover all the causes, even in one country, and there are many countries to consider As has been suggested above, India may be looked upon as a representative tropical country

Without going too deeply into root causes, one can say that the principal common cause of malnutrition is poverty Figures for rural family incomes have been given by various workers, but, as the workers themselves usually claim, these estimates must be taken with considerable reserve on account of the difficulty of applying monetary values, to rural incomes in particular The average family annual income in Bengal has [illegible]

just over Rs 4/— In industrial populations, the monthly income *per capita* is often higher, but this is usually more than counteracted by the higher cost of food and the fact that often little more than half the income is available for food

The cost of the poor and the balanced diets shown in figure 190 would (in normal times, in most places in rural India) be about Rs 2½ to Rs 3 and Rs 5 to Rs 6, respectively, so that very few of the families in the populations instanced above would be able to afford a balanced diet

It has been shown in several investigations in India that, with an increase in the income, not only more calories but a greater proportion of protective substances are added to the diet Thus an improvement in their economic state would not only make it possible for people to purchase a balanced diet, but experience has shown that they will usually do so

This is of course far from the whole solution to the problem as there are many instances in which through ignorance well-to-do persons live on a diet that though adequate in calories is unbalanced, that is, deficient in protective substances, and still others, in India in particular, in which the income is sufficient for them to purchase a balanced diet but they do not in fact do so because their religious or other prejudices will not allow them to take advantage of all the available sources of protective substances Further, malabsorption and/or increased metabolism, that are common to many tropical febrile disorders, increase rather than decrease the patient's general and special dietetic requirements, but such patients are usually kept on a low diet, and therefore frequently show evidence of specific deficiencies This state of affairs which is common in temperate climates (Goldsmith, 1942) is exaggerated in many tropical countries by the local prejudice in favour of starving, not only a fever but any other

TABLE XXVI

Composition and caloric value of some common foodstuffs

Name of foodstuff	Protein %	Fat %	Carbohydrate %	Calcium (Ca) %	Phosphorus (P) %	Iron (Fe) mg %	Vitamin A IU per 100 g	Vitamin B_1 IU per 100 g	Vitamin C mg per 100 g	Calories per 100 grammes	Calories per ounce	Biological value protein
Rice, raw, home-pounded	8.5	0.6	78.0	0.01	0.17	2.8	4	60	—	351	100	
Rice, parboiled, home-pounded	8.5	0.6	77.4	0.01	0.28	2.8	15	90	—	349	99	80
Rice, raw, milled	6.9	0.4	79.2	0.01	0.11	1.0	—	20	—	348	99	
Wheat, whole	11.8	1.5	71.2	0.05	0.32	5.3	108	180	—	346	98	67
Wheat flour, refined	11.0	0.9	74.1	0.02	0.09	1.0	—	40	—	349	99	
Cholam (*Sorghum vulgare*)	10.4	1.9	74.0	0.03	0.23	6.2	136	115	—	355	101	83
Ragi (*Eleusine coracana*)	7.1	1.3	76.3	0.33	0.27	5.4	70	140	—	345	98	89
Maize, tender	4.3	0.5	15.1	0.01	0.10	0.7	42	—	4	82	23	60
Lentil (massur dal)	25.1	0.7	59.7	0.13	0.25	2.0	450	150	—	346	98	41
Red gram (arhar dal)	22.3	1.7	57.2	0.14	0.26	8.8	220	150	—	333	95	74
Soya bean	43.2	19.5	20.9	0.24	0.69	11.5	710	300	—	432	125	54
Amaranth, tender	4.9	0.5	5.7	0.50	0.10	21.4	2,500–11,000	10	173	47	13	72
Brussels sprouts	4.7	0.5	9.2	0.05	0.08	2.3	210	—	72	60	17	
Cabbage	1.8	0.1	6.3	0.03	0.05	0.8	2,000	50	124	33	9	76
Celery	6.0	0.6	8.6	0.23	0.14	6.3	6,000	T	62	64	18	
Lettuce	2.1	0.3	3.0	0.05	0.03	2.4	2,200	90	15	23	7	
Spinach	1.9	0.9	4.0	0.06	0.01	5.0	3 000	70	48	32	9	
Carrot	0.9	0.1	10.7	0.08	0.03	1.5	3 000	60	3	47	13	
Onion, large	1.2	<0.1	11.6	0.18	0.05	0.7	—	40	11	51	14	
Potato	1.6	0.1	22.9	<0.01	0.03	0.7	40	20	17	99	28	67
Sweet potato	1.2	0.3	31.0	0.02	0.05	0.8	10	—	24	132	37	72
Tapioca	0.7	0.2	38.7	0.05	0.04	0.9	—	15	—	159	45	
Sago	0.2	0.2	87.1	0.02	0.01	1.3	—	—		351	100	

TABLE XXVI—(Contd)

Composition and caloric value of some common foodstuffs

Name of foodstuff	Prote n%	Fat %	Carbohydrate %	Calcium (Ca) %	Phosphorus (P) %	Iron (Fe) mg %	Vitamin A IU per 100 g	Vitamin B IU per 100 g	Vitamin C mg per 100 g	CALORIES PER		Biolog ical value protein
										100 grammes	ounce	
Cashew nut	21 2	46 9	22 3	0 05	0 45	5 0	100	—	—	596	169	72
Coconut	4 5	41 6	13 0	0 01	0 24	1 7	T	15	1	444	126	58
Ground-nut	26 7	40 1	20 3	0 05	0 39	1 6	63	300	—	549	156	58
Apple	0 3	0 1	13 4	0 01	0 02	1 7	T	40	2	56	16	
Banana	1 3	0 2	36 4	<0 01	0 05	0 4	T	50	1	153	43	
Mango ripe	0 6	0 1	11 8	0 01	0 02	0 3	4 800	—	13	50	14	
Orange	0 9	0 3	10 6	0 05	0 02	0 1	350	40	68	49	14	
Papaya ripe	0 5	<0 1	9 5	0 01	0 01	0 4	2 020	—	46	40	11	
Tomato ripe	1 0	0 1	3 9	0 01	0 02	0 1	320	40	32	21	6	
Beef (muscle)	22 6	2 6	—	0 01	0 19	0 8	59	50	2	114	32	98
Egg (fowl)	13 3	13 3	—	0 06	0 22	2 1	2 200	—	—	173	49	94
Milk (cows)	3 3	3 6	4 8	0 12	0 09	0 2	180	17	2	65	18	85
Milk (skimmed)	2 5	0 1	4 6	0 12	0 09	0 2		—	1	29	8	
Cheese	24 1	25 1	6 3	0 79	0 52	2 1	—	—		348	99	
Red palm oil	—	100 0					40 000	—		900	256	
Yeast dried	39 5	0 6	39 1	0 44	1 49	43 7	110	2 000		320	91	

form of illness a prejudice which is so deeply ingrained in the minds of the people that the medical man even if he is not tainted with the same prejudice will have great difficulty in persuading his patient to take a better diet

To summarize the principal general causes of malnutrition are therefore poverty and ignorance and as a corollary the first two general measures of prevention will be improvement of economic status and education

Measures of prevention —Improvement of economic status is outside the scope of the medical profession and our duty as ordinary medical men or women in this matter ends when we have demonstrated to the statesman *(or the administrator) and the agriculturist the* correlation between poverty and malnutrition in any particular country or community though a constant liaison between the agriculturist and nutrition specialist is essential

But in the matter of education our duty is much wider Medical education has been backward in the teaching of dietetics and it is first necessary to make up this ground by impressing on the medical man of both today and tomorrow the importance of a sound knowledge of the principles of dietary this applies more especially in the tropics where the subject is relatively much more important than in temperate climates (It is on these grounds that the present writer excuses himself for including in the chapter much that all practitioners should and the majority of readers probably do already know) The next person to be educated is the administrator whether he is a government administrator or the manager of a labour force Here the advice given must be accurate and based on locally obtained data uncontroversial and practical or it will carry no weight

Direct education of the population will not be the doctor s work this must be done through lay health workers and school teachers but it is the business of the medical profession to see that these people understand properly what they have to impart * Where there is a public health department this should include a nutrition officer whose duty will include amongst other things education and propaganda

In addition to these long term nutrition policies it will often be possible to do something more immediate for special groups The most critical periods when the physiological demands are greatest are during pregnancy and lactation and in childhood Where maternity and child welfare organizations exist much can be done by advising mothers and giving milk and other protective dietetic substances to both mothers and infants and the school child s home diet can be similarly supplemented during school hours as is done in many western countries Skimmed milk made *from* imported powder which is cheap and has a high pro in content is worth considering for this purpose also soya bean preparations When synthetic vitamin preparations become cheaper as they probably will it may be worth ensuring that mothers and children get an adequate supply of all necessary vitamins by giving these to them in pill form and even today it is often worth giving pregnant women iron in the form of ferrous sulphate tablets or a mixture

* h h f om the government of Ind a Publ cat ons of th s kind if they are not these *two*

In the treatment of his own patients the doctor has a special responsibility He should always ensure that his patient's diet is adequate in all the vitamins remembering that the requirements in the febrile conditions in particular may be above those of a normal person He should be especially cautious when his patient is subsisting on a milk diet, which is almost devoid of ascorbic acid and iron, and very low in niacin, and when nutrition is maintained largely by intravenous glucose, in which case thiamin will be an additional requirement

Special problems, such as that of rice, and measures directed against specific deficiencies are discussed under the appropriate deficiency diseases

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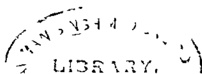
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BERIBERI

INFANTILE BERIBERI

Definition —Beriberi is a metabolic disorder characterized by peripheral neuropathy, myocardial weakness and frequently œdema occurring in persons on a diet deficient in vitamin B_1

Historical —The syndrome known as *kakke* or leg disease was described in early Chinese literature several hundred years before the Christian era The name beriberi appeared later and seems to have been derived from a Malayan word *biribi* meaning a jerky gait or from an Indian word *bharbari* meaning a swelling In Japan it was known by the Chinese name *kakke* and was described by early

as occurring in the Dutch East
ical me h ine reported it in Ind a
the western hemisphere appeared
en it was reported in Brazil and

and

EPIDEMIOLOGY

Geographical distribution —The disease has no geographical limitations It was for many years looked upon as a purely tropical disease but this was shown by an outbreak in Newfoundland to be a wrong conception and since then isolated cases have been reported in nearly every country in the world However as at least ninety per cent of cases occur amongst rice eating people the distribution of the disease is mainly tropical the largest number of cases have been reported from China Japan (an annual average of 17 000 deaths between 1920 29) Indo China Siam Malaya and the Dutch East Indies the Philippines India tropical and South Africa also Brazil and the West Indies Small outbreaks have occurred amongst the natives of Western Australia in Newfoundland and Labrador, in Iceland and in institutions in the United States Great Britain, France, and Holland

In **India**, some confusion has arisen through the popular practice (which is unfortunately sometimes encouraged by medical writers) of referring to epidemic dropsy as beriberi but it is now generally accepted that the only area where the beriberi assumes serious proportions is the north-east coastal area of the Madras Presidency the Northern Circars (*see* figure 192)

Epidemiological status —It is not a truly epidemic disease (*see* p 324) but the appearance of outbreaks that involve a large number of persons living in close contact and of course always on the same diet, give the semblance of an epidemic Nor as far as is known is it in any way dependent on local conditions except in so far as these affect the food supply of the population As noted above it occurs mainly in native populations whose staple food is milled rice It has also appeared in armies labour forces and amongst the inmates of institutions similarly fed, and has disappeared when the diet has been changed to under milled rice, or some suitable supplement has been added Outbreaks not associated with milled rice have been reported amongst people who have lived for some

time on a monotonous diet with white flour as the staple substance *e g* in Newfoundland, where the diet was almost solely white bread and molasses for certain months of the year, and in institutions, usually mental asylums where white bread was used It has also occurred on ships where



Figure 192 Map showing distribution of beriberi in southern India in 1938 and the number of cases of beriberi treated in each district during that year (Aykroyd et al, 1940)

ships biscuits made from white flour and tinned foods have been the principal diet

It is a disease of towns rather than rural areas

Seasonal incidence—In most places where the disease occurs there is some season during which it is most prevalent, but this is not by any

means the same season in different places Much capital has been made out of this seasonal incidence by the champions of different theories who can usually find from the varied data some that suit their particular theory For example in the Godavari delta (Southern India) the incidence of beriberi is high in September and low in January, this no doubt would be attributed to the stored rice becoming damp during the monsoon, by the supporters of the rice infection or rice toxin theories but Aykroyd and Krishnan (1941) find quite a different explanation namely that when the rice is freshly harvested at the end of the year it is not suitable for consumption unless it is first parboiled so that in this district 56 per cent of the rice eaten in January is parboiled whereas in September the last year's crop is mature and can be eaten without previous parboiling, and only six per cent of rice eaten in this month is parboiled * In nearly every case the seasonal incidence can be similarly explained in terms of the present theory of the ætiology of the disease (*vide infra*)

Age, sex, and race incidence —In a mixed population the disease is undoubtedly less common in children than in adults though it does occur amongst the former There is also a form of infantile beriberi that occurs in the breast fed infants of mothers with beriberi More men than women are affected, but there is little evidence of any true sex preference except that possibly in the working labourer the caloric requirements are greater he will eat more rice, his vitamin B_1 requirements will be correspondingly greater and he is therefore more likely to show evidence of the deficiency The more probable explanation is however that there are usually more men than women in the type of population that is affected

There is little evidence that any one racial type is more susceptible than any other, the fact that European personnel of institutions escape the disease when native soldiers or native inmates suffer can of course be explained on the differences in their dietary

ÆTIOLOGY

Historical —The story of the discovery of the cause of beriberi forms an important part of the story of the discovery of the vitamins

The first worker to recognize the dietetic nature of beriberi was Takaki In 1884 he rec
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In 1890 and the two succeeding years Professor Eijkman working in a laboratory in Batavia that had been established for the study of beriberi produced 'polyneuritis' in fowls by feeding them on polished rice and cured it by giving th
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ia carried the work further and came to
the absence of some essential ingredient
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and in government institutions in Java

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In 1909 Fraser and Stanton carried out some planned feeding experiments with Javanese labourers they confirmed the above observations but also showed by interchanging the experimental groups that locality had no influence on the devel

* Parboiling saves the vitamin B_1 see p 757

opment of the disease and that it was not transmissible from one man to another They also carried out experiments with fowls that showed in addition to the facts already elicited by previous worker that storage in a damp place had no detrimental influence on rice vis-a-vis beriberi but that if the whole rice grain was subjected to autoclaving at 130°C for an hour it would produce polyneuritis in birds in exactly the same way as polished rice, this experiment incidentally also showed that no living infective agent in the rice was responsible for the disease Other confirmatory experiments were carried out by Strong and Crowell (1912) and by Vedder Casimir Funk, working at the Lister Institute isolated a pro- the word vitamine alline vitamin B was nthesized by Williams

Many other theories were advanced regarding the nature of beriberi Several so-called causal organisms were isolated and the theory that badly stored rice developed some special toxin was strongly supported although this last theory

The present position—It is generally accepted today that the essential ætiological factor in the syndrome beriberi is a deficiency, absolute or relative, of vitamin B_1, the pure form of which is known as thiamin or aneurin Whenever the disease has occurred in a community, it has been possible to show that the staple food was milled rice or some other cereal which in its preparation has been deprived of the bulk of its natural vitamin B_1 alteration of the diet so that it includes an adequate amount of this vitamin has always led to the disappearance of the disease from that community, and administration of large doses of the vitamin will always cause a disappearance or at least marked improvement in the specific symptoms of individual sufferers

In a community in which there is a low intake of vitamin the individuals most likely to suffer from beriberi will be those who take an exceptionally large amount of carbohydrate, pregnant and lactating women hyperthyroid individuals and subjects with febrile diseases all of whose normal requirements of vitamin B_1 are increased

Sporadic instances of beriberi, if they cannot be explained on the grounds of actual deficiency of vitamin B_1 in the food taken as in the case of long continued dietary restriction or of chronic alcoholism when the appetite is dulled and alcohol itself acting as a pure carbohydrate provides a large proportion of the calories, can be traced to malabsorption ... chronic ... hese

Thus to summarize, the causes of this disease are (*a*) absolute deficiency of vitamin B_1 in the diet, (*b*) a deficiency relative to the special requirements of the individual (*c*) failure of absorption of vitamin B_1 and (*d*) failure of storage and utilization

It is frequently claimed, especially by workers who still have a leaning towards some of the earlier discarded theories, that the deficiency of vitamin B_1 is not the whole story of the ætiology of beriberi This is of course very probable, one might almost say quite certain as what single ætiological factor is the whole story of any disease? In an infectious disease there is always the seed and the soil to be considered, similarly in

an induced metabolic dysfunction both the patient's previous metabolic state and superimposed infections may well help to determine morbidity Further it is probable that if one vitamin is deficient others will also be deficient and these other deficiencies may contribute to the clinical picture And having decided that it is purely an avitaminosis do we know how a deficiency produces a disease and can we entirely discard the pos

Vitamin B requirements —The figure usually given is 330 to 660 international (IU) or 1 to 2 milligrammes The higher figure will include such special classes as pregnant and lactating women However it has recently been shown that the vitamin B requirements vary according to the carbohydrate intake and it is now usual to express the vitamin B_1 requirements in terms of the calorie intake it is suggested that the lowest safe amount is 0 25 IU per calorie (Williams and Spies 1938) which in the average man will be above the maximum indicated above However when most of the calories are from carbohydrates this figure will not be too high Fat spares vitamin B and when the latter is deficient the body fat is drawn upon to reduce carbohydrate metabolism to a minimum when this vitamin is exhausted carbohydrate metabolism increases and symptoms

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The work of Mills (1941) with rats suggest that tropical conditions may increase the requirements of vitamin B This is interesting in view of the fact that beriberi is common on in tropical countries but it should be confirmed with other animal species and by human experiments in view of the contradictory fact that tropical heat reduces basal metabolism

Sources of vitamin B —The best sources of this vitamin are pork whole grain cereals and their products beans and peas yeast and liver Although milk meat other than pork and fruit do not contain much vitamin B_1 it is present in small quantities in most natural foodstuffs It is however often discarded or destroyed in the preparation of these for consumption *e g* in the milling of rice and other cereals in cooking and in canning It is destroyed by heating to 130° C in one hour it however, withstands boiling in an acid medium but is destroyed in an alkaline medium

Recent work (Najjar and Holt 1943) suggests that in certain circumstances thiamin may be synthesized in the human intestinal canal The implications of this observation are very great and although it is not clear what determines the synthesis it seems likely that the nature of the staple diet or of other non vitamin dietary factors may have some influence

For further details regarding the source of this vitamin the reader is referred to the tables and discussion on rice in the previous chapter

PATHOLOGY

Morbid anatomy —The whole body is wasted and all subcutaneous fat has disappeared this may be masked by œdema There may be gen

eralized **œdema** with fluid in the *serous cavities* This œdema is not necessarily due to cardiac failure as it often occurs in a person with a competent heart but to a breakdown *in the mechanism* that controls the interchange of fluids and maintains the water balance of the tissues it is more marked in the more acute cases The changes *in the* **peripheral nerves** are degenerative [illegible] *neuritis* is inappropriate *the sciatics* and their branc[illegible] e rarely the cranial nerves [illegible] *ons vary in* their extent according to the severity and duration of the affection there may be barely de[illegible] sheath only with of some of the ax[illegible] whole nerve

As well as the peripheral nerves scattered fibres in the tracts cells of the anterior and posterior horns and the sympathetic ganglia are affected [illegible] d nerves show atrophic changes There is [illegible] ularly of the right side of the **heart** [illegible] *is often associated with heart* failure and death)

Microscopically the most striking feature is intercellular œdema There is also fragmer[illegible] necrosis of the cells its effect on the cells but it is possible that both factors operate)

Biochemistry—*Vitamin B is absorbed in both the small and the large* intestine It is stored in the liver and kidneys but it is also found in other organs and tissues It is excreted in the urine and the amount excreted is a good indication of the vitamin B_1 state of the organism in health the average daily excretion in an adult is 20 to 30 IU being higher in men and this may fall as low as 3 5 IU in beriberi The vitamin B [illegible] + 2 γ or about 2 to 4 IU per [illegible] ood indication of saturation [illegible] goes to show that vitamin [illegible] f carbohydrate and controls [illegible] t is certain that the vitamin B requirements vary according to the carbohydrate intake It is suggested that this intermediate product is (at least in the case of some carbohydrates *e g* rice) of a toxic nature

It has been found that the pyruvic acid in the blood and body tissues varies inversely with the vitamin B intake The normal level of pyruvic acid *in* the blood is 0 5 to 1 0 mg per 100 grammes it rises considerably in acute cases of beriberi but is restored to normal by vitamin B_1 administration In more chronic cases it may be demonstrably increased A sharp and prolonged rise in the blood pyruvic acid after intravenous glucose constitutes a useful test for vitamin B deficiency

The urine—This will not show any characteristic changes It will be scanty and there may *be anuria during the severe cardiac attacks* On resumption of the flow there will be a heavy cloud of albumin and granular casts *The vitamin B content* has been discussed above

The blood picture—There is often a marked macrocytic anæmia Although this may be due to associated deficiencies the writer has seen cases

in which the anæmia appeared to respond specifically to thiamin chloride injections The lymphocytes are reduced and in the infantile form small lymphocytes may be absent

SYMPTOMATOLOGY

Introduction —The beriberi syndrome is a clear cut one, quite distinct from any other recognised syndrome but nevertheless as in almost any disease there are distinct clinical types the distinction being due to the predominance of different symptoms which in turn are dependent to some exten ...

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or wet form and (c)
The acute fulminating f
from the wet form he may pass into the chronic form There will of course be obvious cases of beriberi that will defy accurate classification

It is usually about three months after the diet has become deficient in vitamin B_1 that the first symptoms appear if the deficiency has been very complete the time may be shorter

The fulminating form —After perhaps a few days of prodromal symptoms such as anorexia gastro intestinal disturbances easy fatiguability or in some cases without any warning the patient becomes breathless and cyanosed he complains of severe epigastric or substernal pain and often vomits he may also suffer from aphonia (the result of pressure by the right auricle on the recurrent laryngeal nerve) His heart is greatly dilated the veins in the neck stand out and the liver becomes large tender and pulsating The systolic blood pressure is usually lowered and the diastolic very low indeed The patient dies suddenly within a day or so of the first onset of symptoms with acute circulatory collapse

The œdematous form —In this form the onset is a little more gradual after a short but definite period of ill health often with gastro intestinal symptoms there is a gradual onset of œdema with tiredness and shortness of breath on exertion The œdema at first only in the extremities gradually extends until it involves the trunk eventually there is general anasarca There are usually some symptoms of peripheral neuropathy but as the other symptoms confine the patient to his bed they are easily overlooked wasting is masked by the œdema

The heart is usually dilated the apex beat is diffuse and fluttering the pulse is soft and rapid the veins in the neck are prominent the liver is enlarged and tender and the pleural cavities fill with fluid but usually the lungs remain clear until a terminal œdema develops The blood pressure falls as in the acute form with the relaxation of the peripheral tension an injection of adrenalin further lowers the diastolic blood pressure almost to zero but pitressin causes a rise in blood pressure that is maintained for an hour or so The electrocardiogram may show right axis deviation and flattening of the T waves also prolongation of the Q T interval and a low QRS complex

The chronic, polyneuropathic form —The onset of this type is far more gradual and for some weeks the patient may struggle on with his

work complaining of loss of weight, weakness, slight breathlessness on exertion headache and vague pains, stiffness and lameness of the legs The only objective symptom may be tachycardia The condition increases and he becomes less able to carry on his work He now complains of numbness and a burning sensation of the feet as well as stiffness of the legs and he finds difficulty in rising from a sitting posture, the calf muscles are tender on pressure and areas of hyperæsthesia appear which later become anæsthetic, knee jerks which were at first slightly exaggerated now disappear and so do the ankle jerks The definite characteristic ataxic high-stepping gait appears The condition then spreads to the upper limbs, there is wrist drop, wasting of the hands and fore arms and incoordination of the movements of the hand so that the patient drops things easily and is unable to pick up small objects Chvostek's sign (fibrillary tremors of the muscles on being tapped) may be present

The muscles of the limbs become wasted and show the typical reaction of degeneration The patient gradually becomes emaciated, helpless and bed-ridden The sphincters are usua"
dition remains clear There is usually
increases of cardiac symptoms otherwi
mains good but he may die of hypostatic pneumonia or some other complication

Irreversible changes take place in the nerves, contractures occur in limbs and even if he lives the patient becomes irreparably crippled

Sporadic or conditioned beriberi *—The beriberi that occurs in well fed populations in special individuals *e g* pregnant women alcoholics etc (*vide supra*), usually takes the chronic peripheral neuropathy form but with recognisable cardiac signs and symptoms, and quite often a variety of other symptoms suggestive of neurasthenia However, acute cardiac attacks have been reported

Sub-clinical beriberi—Positive evidence of a fact already assumed by many workers, namely that in a population in which there are many cases of beriberi there will be many other persons on the threshold of clinical avitaminosis, is rapidly accumulating, now that biochemical tests for this vitamin are within the scope of the medical investigator—even if not of the ordinary practising physician and there are several relatively simple clinical tests (*vide infra*) Although these minor degrees of B_1 avitaminosis may be classed as sub clinical, if the person is examined and questioned carefully, some of the minor signs and symptoms *e g* tachycardia, breathlessness on exertion anorexia stiffness and vague pains emotional instability and mental depression may be elicited

DIAGNOSIS

This can be considered under a number of headings —

(*a*) The patient's environment diet and habits
(*b*) The clinical picture

* The writer has avoided the word *secondary* because he considers it misleading and believes that eventually it will be dropped It is extremely probable that in any outbreak of beriberi in a population living on a diet deficient in vitamin B_1 morbidity is determined by some secondary factor in nearly every case whether it be slight hyperthyroidism a febrile infection *e.g* malaria or the consumption of a larger amount of rice than the rest of the population It would be unreasonable to consider such cases *primary* whilst labelling as *secondary* a case of beriberi associated with pregnancy

(c) Clinical tests including the therapeutic test
(d) Biochemical tests

Little further need be said about (a) and (b) It is unlikely that an outbreak of œdema or neuritis in a poorly fed population would fail to arouse one s suspicion but sporadic cases very often will in fact, there is evidence that until a few years ago the majority of such cases were wrongly diagnosed The conditions for which they may be mistaken are considered below

(c) Of the **clinical tests,** the most valuable is the therapeutic test but it is very liable to be misleading in that in so many conditions a B avitaminosis may be superimposed on some other condition so that immediate improvement on administration of thiamin chloride does not provide the whole answer conversely where there are other deficiencies besides tho e of vitamin B the slowness of the improvement after the administration of the pure vitamin does not altogether exclude beriberi However a few doses (ten may be considered the maximum) or even a single dose of 10 milligrammes given intravenously will often produce dramatic improvement in the leading symptoms This applies especially to the cardiac condition in the polyneuropathic form the improvement will be slower and in advanced cases of nerve degeneration there will be none

Other tests for vitamin B saturation have been suggested In a case of deficiency adrenalin will cause a further sharp fall often to zero in the already low diastolic blood pressure or as a variation the rise—if rise there is—in systolic blood pressure after the administration of adrenalin will be greater if a large dose of thiamin chloride has been given previously Another test is associated with the diuretic effect of thiamin in the deficient individual this is considerable Finally the circulation time which is usually prolonged in cardiac failure is normal or decreased in beriberi

(d) Of the **biochemical tests,** the best indication is obtained from the excretion of vitamin B in the urine the average daily excretion in a normal person is from 20 to 30 IU and in a patient with beriberi about 3 5

variation After
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able that easier and more satisfactory tests will be devised

Differential Diagnosis—The neuropathies have to be distinguished from those of arsenic lead triorthocresyl phosphate (jake) and other poisons from diphtheritic paralysis from rheumatism and various myo

The œdema has to be distinguished from that of kidney and organic heart dis

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In most of these conditions if the case is a typical one there are one or more characteristic signs or symptoms that will differentiate them sharply from beriberi enumeration of these does not seem to be called for here

PREVENTION

This can of course be summed up in the single sentence 'increase th intake of food rich in vitamin B_1 There is however more to be said o the matter than this Let us first take the sporadic case this usuall presents little difficulty In conditions such as pregnancy, hyperthyroidism it is advisable to recommend the regular taking of extract of yeast or ric polishings or some medicinal form of vitamin B_1 as well as food rich i this vitamin (*vide supra*) This also applies to patients put on to a re stricted dietary for any reason In gastritis or pernicious vomiting it advisable to give the prophylactic thiamin chloride parenterally

The real problem is the prevention of beriberi in large and poor popu lations T ... cussed in

with this disease As was noted ... occurs amongst rice eating people Th whole edible portion of the rice grain contains quite sufficient vitamin B to ensure the proper metabolism of the whole grain but when the grain is milled in the raw state much of the vitamin is lost and when it i washed and cooked and the water discarded more of the already deplete vitamin is wasted Parboiling prior to husking saves most of the vitamin If therefore people will first parboil their rice, home pound it instead o allowing it to be over-milled clean it—if this is necessary—in the dry state cook it with the minimum of water and utilize the rice water in their food beriberi will not occur In populations where milling has been established for some time there are many practical difficulties in institut ing this ideal procedure which are dealt with on p 758 where also a com promised procedure of limiting the degree of milling is discussed

The same problem has to be faced in the case of other cereals the case of white flour, which is also deficient in vitamin B_1 but which for æsthetic and other reasons is often preferred has been met in some coun tries by 'fortifying' the white loaf by the addition of synthetic thiamin chloride

TREATMENT

The treatment can be considered under three headings specific die tetic, and symptomatic It may be argued that the specific and the dietetic treatment cannot strictly speaking be separated but, as in many cases it will be advisable to give thiamin chloride in addition to any special diet ... a chem ... dramatic ... ider it as

Specific—It will naturally not be possible to give thiamin chloride to every member of a large community in which the majority of the people are suffering from either frank or sub clinical beriberi nor in a large per centage of the ca ... all frank cases of beriberi thiamin chloride ... as possible for one can seldom be c ... denly become acute It has been shown that the best results are ... when generous doses are given and for an adult a daily dose of at least 20 mg should be given either intramuscularly or intravenously for ten days to a fortnight after this the dose can be reduced considerably or thiamin (10 mg) dried

Brewer's yeast (6 ounces) or marmite (or vegex) (2 ounce) can be given by mouth Infants can be given 3 mg of thiamin chloride daily with safety in fact it is very doubtful if there is any limit to the dosage In acute cardiac cases doses of over 100 mg have been recommended but the writer believes that 25 mg is about the maximum effective dose The development of sensitivity to thiamin chloride has been reported so that there may be danger in intermittent parenteral treatment The dose should be not spaced too widely and if treatment has to be restarted after an interval a small test dose should be given first There is much to be said for combining the parenteral thiamin with yeast extract as the latter contains other vitamins particularly those of the vitamin B complex group that are probably also in deficit

Dietetic —Rice should be excluded from the diet at first because of its high carbohydrate content but also because of the possibility that intermediate products of metabolism of the rice carbohydrates may be especially toxic The patient should be put on a diet composed of substances low in carbohydrate and high in vitamin B content such as egg yolk liver pork oatmeal peas beans cauliflower parsnips radishes nut and soya beans Later milk whole meal bread or other whole grain cereal and any substance other than rice that he normally includes in his diet may be added or substituted and eventually he may be allowed to return to his rice diet but it must be undermilled and parboiled and the addition of vitamin B_1 containing substances should be recommended

Symptomatic —In the severe cardiac case the patient must be confined to bed put on a light solid diet with the fluid intake reduced to a

nergency Præcardial pain
be necessary to let a little
this should be avoided if
be embarrassing the heart

should be removed A saline purgative should be given Intravenous thiamin in large doses as recommended above will usually produce diuresis reduce the œdema and relieve the heart but if anuria continues one

sorted to Digi
trophanthus has
Oxygen given

Little can be done to relieve the neuropathy beyond the specific and dietetic treatment but massage and electrical treatment will help to maintain the tone of the muscles until the nerves recover It may be advisable to use splints to prevent wrist and foot drop

PROGNOSIS

In fulminant cases either adult or infants the prospect is usually hopeless in any case in which there are cardiac symptoms it is bad but immediate and efficient treatment may save the patient and in the severe neuropathic cases permanent disability may result but in the earlier cases when only a few nerve fibres have degenerated suitable treatment will lead to complete recovery

In the acute cardiac attack in sporadic beriberi where there is no background of long continued vitamin B_1 starvation, there is often a dramatic response to large parenteral doses of thiamin

INFANTILE BERIBERI

Most of the evidence suggests that this disease is the same as adult beriberi but there are special epidemiological and clinical features that make it more convenient to discuss the infantile form separately

EPIDEMIOLOGY

It occurs in the infants in a population living on a diet low in vitamin B_1 content and usually in one in which there are numerous cases of adult beriberi The highest incidence is in the second to the fourth months of life in infants that are entirely breast fed but it also occurs in infants that are partly breast fed or even not breast fed The mothers are usually found to be suffering from minor degrees of chronic beriberi but they may show no clinical evidence of beriberi at all It is believed that the particularly high infantile mortality in countries subject to beriberi can *be attributed to the high incidence of infantile beriberi This has recently* been emphasized by Aykroyd and Krishnan (1941a) who have carried out a survey in the Northern Circars district of Madras one of the worst beriberi areas in southern India and have shown that the peak of the infantile death rate curve in this and other beriberi districts is not as is usual at the first month, but at the second to the sixth months

ÆTIOLOGY

There are two schools of thought on the ætiology of the disease both point out that in order to allow for the low intake of vitamin B_1 in the first few months of life the fœtus must store the vitamin as it does iron but in this case unlike that of iron where the infant drains almost the last milligramme from its mother both mother and child share the deficiency The adherents of one school however believe that the beriberic mother secretes some toxic intermediate incompletely oxidized product of carbohydrate metabolism which is neutralized by the infant's store of vitamin B_1 until the latter is exhausted while the adherents of the other school e g Vedder believe that the already low vitamin B_1 level of the infant of a beriberic mother is lowered still further to the clinical threshold by the particularly low vitamin B_1 content of the beriberic mother's milk (Sundararajan (1941) has shown that the vitamin B content of the milk of beriberic mothers is not consistently low but in any case the vitamin B *calorie coefficient of human milk is much below the necessary 0 25 IU)*

Clinical picture—Several classifications have been suggested but for practical purposes the cases can be divided into acute and chronic The **acute** form usually occurs in breast fed infants within the first three months of life after a short period of anorexia and restlessness *or in* some cases without any previous warning the infant has convulsions vomits becomes cyanosed and dyspnœic cries out with acute pain if it *is not aphonic, and dies of* acute heart failure within as short a time as a few hours in fulminating cases In the **chronic** form there are gastro intestinal disturbances wasting aphonia and dysphagia and generalized œdema The chronic form may terminate suddenly with a fulminating attack and more rarely *an acute attack* subsides and becomes chronic

PREVENTION AND TREATMENT

Preventive measures applied to the whole population will naturally prevent this disease in infants but any special measures must be applied

to the mother as well as to the child In beriberi districts the diet of even apparently healthy mothers should be supplemented by B_1 concentrates

The first step in treatment is to take the infant off breast feeding and to give it a diet rich in vitamin B_1, but it will also be necessary to add concentrates either recognised commercial concentrates, or some more homely substance such as *tiki-tiki*, which is an extract of rice polishings made by absorbing vitamin B_1 on acid clay In acute cases the parenteral administration of thiamin in 1000 IU doses is recommended

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PELLAGRA

Definition —Pellagra (*pelle* = skin *agro* = rough) is a non infectious disease occurring in epidemic like outbreaks mainly in poor populations whose staple diet is maize and also sporadically in other population groups It is associated with a deficiency of vitamin B complex especially of niacin in the diet and it is characterized by gastro intestinal disturbances dermatitis mental deterioration and eventually if the disease is uncontrolled death (The mnemonic five D s—namely Deficiency Diarrhœa Dermatitis Dementia Death—is applied to it)

country after another accord ng to early med cal histor ans who of course may have been prejudiced by their incl nation towards the maize theory of the origin of pellagra In 1776 pellagra assumed serious proportions in Italy and legislat ve action was taken to control the sale of maize on th s account A century later

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EPIDEMIOLOGY

Geographical distribution —The disease has a wide distribution in the temperate sub tropical and tropical zones it is a disease of poor and backward countries rather than of hot ones The association of the disease with maize as a staple diet is responsible for its higher incidence in subtropical countries

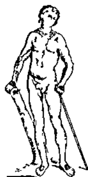


Figure 193 Patient suffering from *mal de la Rosa* (pellagra) From Casal s *Memorias de Historia Natural de Asturias* (1762)

As well as those **European** countries already mentioned other Southern European countries have suffered considerably from the disease in 1918 it was estimated that there were 70 000 cases in Roumania and further east in Transcaucasia three to four per cent of the whole population were affected and in France Germany Denmark and other northern European countries it occurs sporadically In **Africa,** it is not uncommon in the Mediterranean countries from Morocco to Egypt in the Sudan and Abyssinia and amongst the Kaffirs and Zulus in central and southern Africa In **Asia,** it has been reported from Syria and Asia Minor China the East Indies and the Philippines and Japan *In **India,** Lowe (1931) drew attention to it at a leper* asylum and since this date sporadic cases and small outbreaks have been reported from many parts of India In Calcutta we have diagnosed about a dozen cases a year all sporadic for several years past

In the **Western Hemisphere,** it was estimated that in 1916 there were 150 000 pellagrins of whom about 10 per cent died It is still endemic throughout most of the southern United States today Isolated cases have

been reported in Canada, and the disease is also common in Central and South America

A few cases have been reported in Australia

Epidemiological status —Throughout its whole history the disease has been associated with *maize* and the largest and most characteristic outbreaks have always occurred amongst people whose staple diet is maize Outbreaks have however occurred amongst people living on rice and other cereal diets, and in the m[illegible]
dietary can [illegible]
can be trace [illegible]
cases, and r [illegible]
living in sch[illegible] [illegible] food was plentiful and varied

In more prosperous countries the only outbreaks are in institutions usually mental institutions, where the food is liable to be so monotonous that the inmates do not eat all *that is given to them* It is also not un common in prison camps, when food is short, but like beriberi it does not often occur during *famines*

It has been reported amongst patients who have been placed on a restricted diet for medical reasons and who have continued this diet for long periods without reference to their medical advisers (milk and eggs *are a very poor source of the* pellagra-preventing factor) and it also occurs amongst alcoholics, the ætiology in this case is not clear, but it is probably associated again with a low dietary intake—common amongst alcoholics—or to a lowered absorption through the associated gastritis

Seasonal incidence —It shows definite seasonal incidence although the season is different in different countries it is constant in any one country In cool countries it occurs in the autumn, and in hot countries in the cooler months of the year The explanation of this apparent anom aly is that sunlight plays an important part in the ætiology, in the former countries there is more sunlight in the summer months and in the latter people tend to avoid the sunlight in the hottest months whilst exposing themselves in cooler months It is noticed that people susceptible to the disease suffer from an exacerbation of symptoms at the same time each year but that in pellagra endemic areas there are ' bad ' years and ' good years

Age, sex, race, and occupational incidence —It occurs at all ages from three months to a hundred years', in some populations children seem to be less affected but this is not universally true

There is very distinct female predominance in some places in Rou mania the sex ratio males to females, was said to be as low as 1 to 3 In India also we have found more females affected but in some other countries it is reported to be more common in men and the reason given has been that they work harder

There is little evidence of any true racial selectivity Jews have been reported as seldom affected but here the occupational factor probably comes in

The disease is undoubtedly much more common in outdoor workers particularly agricultural labourers than amongst clerks and indoor work ers on comparable diets, both hard work and sunlight are predisposing factors

ÆTIOLOGY

Historical—The earliest theorists associated pellagra with maize but as all

In 1913 Goldberger and his coworkers in the United States demonstrated that the disease could be eliminated by giving diets with a higher protein content and for a time he considered that it might be due to the general protein deficiency of a maize diet or to a deficiency of some specific amino acid that did not occur in the proteins of maize Later however when he found that it could also be prevented by a yeast preparation that was practically protein free and had been heated to destroy the heat labile vitamin B_1 fraction he revised his earlier opinion Eventually the pellagra preventing (PP) fraction of vitamin B was further broken down into riboflavin nicotinic acid afterwards called niacin etc (see p 763) and Elvehjem demonstrated that niacin would cure pellagra It has been confirmed by many workers that in most cases the administration of niacin will effect a complete cure of pellagra in a very short time Niacin was first synthesized in 1879 and was isolated from rice polishings by Funk in 1911 but discarded by him because it did not cure beriberi

This is not however the end of the story of the ætiology of pellagra which many people still believe to be an unsolved problem before discussing the position as it stands today it will be as well to review the various theories that have been put forward

(i) **The maize infection theory**—It has been suggested that in cer

experimental support for this theory

(ii) **The maize toxin theory**—The neurological changes that occur appear to be of toxic rather than bacterial origin and support has recently been given to this theory by the occurrence of pellagra amongst individuals taking maize alcohol but there is no evidence experimental or otherwise to indicate the actual nature of this toxin and attempts to isolate it have failed Further many people have taken maize as their staple diet all their lives and have never suffered from pellagra and yet others who have never taken maize suffer from it

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rays as ergosterol is converted into vitamin D but here again support for this theory is lacking

(iii) **Protein deficiency**—This theory is dependent on the fact that all pellagra producing diets are low in protein content Maize has a low

protein content compared with other cereals, and, further, the biological value of the protein is also very low The two facts combined make maize a very poor source of good protein

(iv) **Specific protein or amino-acid deficiency**—Maize is defective in protein not only quantitatively but qualitatively, and there are for example certain important amino-acids absent from maize protein or zein *e g* tryptophane and lysine It was suggested that some such specific deficiency is the cause of pellagra

(v) **Vitamin deficiency absence of the PP factor from the diet**—The PP (pellagra-preventing) factor is part of the vitamin B complex which contains amongst other vitamins, niacin, lactoflavin or riboflavin and pyridoxin (B_6 or anti-dermatitis (rat) factor) Food that is rich in vitamin B_2 such as yeast, meat, and liver extract, rapidly cure uncomplicated pellagra, even in patients who are left on their otherwise pellagra producing diet More recent work, referred to above, has identified niacin as the specific PP fraction, and the synthesized vitamin will control many of the specific symptoms of the syndrome

For this theory support has been obtained from animal experiments Dogs fed on pellagra-producing diet develop a condition known as black tongue' this condition clears up rapidly when vitamin B complex is added to the diet, and is considered to be analogous to pellagra in man It has
i B complex that is specific
of vitamin B_2 complex are
the dermatitis produced in
itamin B_2 complex which,
though it has been named 'rat pellagra , is apparently not analagous to the human disease does not respond to niacin, but improves when vitamin B_6 is given

The present position—This can best be stated by first enumerating some of the established facts

(a) Niacin in suitable doses will effect a complete and dramatic cure in most cases of pellagra but of course the condition is likely to return unless the patient changes his diet

(b) In other cases, niac ... nt and
cure his skin lesions but w
require for their cure the
riboflavin for the cheilosis
neuropathy

(c) In yet other cases of apparently typical* pellagra niacin has no beneficial effect at all some of these patients respond to liver extract but others are totally refractory

(d) Analysis of foods for their niacin content has brought to light many anomalies *e g* Aykroyd and Swaminathan (1940) have shown that the rice diet taken by many millions of people in India is a much poorer source of niacin than the maize diet of certain pellagrins However, some workers question whether at present chemical methods of estimating niacin in foodstuffs are sufficiently accurate to base any important conclusions on such estimations

*Some workers deny the fact that the true pellagra syndrome ever fail to respond to niacin given both orally and parenterally

are required

The complete explanation of (c) does not seem possible on known facts and necessitates introducing a more hypothetical explanation it has been suggested that there is an intrinsic and an extrinsic factor the latter being niacin and the former not, of course the same as the intrinsic factor deficient in pernicious anæmia but closely related to it, for all pellagrins shows achlorhydria or hypochlorhydria There is certainly evidence that the individual make up of the patient *e g* his endocrine balance determines *to some extent the onset of pellagra* in one person and not in another on a similar diet and probably also the response to treatment Cases have been reported which suggested the existence of antagonistic action between thiamin and the PP factor (Lehmann & Nielsen 1939) The writer has recently reported a case (Napier & Chaudhuri 1943) in which pellagra was apparently controlled by means of thyroid extract Is it possible that the antagonism lies in the fact that beriberi is associated with hyperthyroidism and pellagra with hypothyroidism?

Observation (*d*) is puzzling It seems to the writer that no explanation of the ætiology of pellagra can be accepted that does not take into consideration the past and present predominance of the disease amongst people whose staple food is m
which by itself is not
tion with the vitami
amount of niacin is c
when this is present in a diet the normal requirements of niacin are increased As alternatives to the theory of a toxin produced by the effects of external agents *e g* bacteria on the maize grain it is possible that some intermediate product of metabolism of maize protein or maize carbohydrate is toxic or at least capable of fixing the niacin or to carry theoretical considerations further that niacin may be synthesized in the intestinal tract under certain conditions (*c f* the synthesis of thiamin (Najjar and Holt 1943) which a maize diet does not favour

In conclusion, putting aside theoretical considerations one can say that the exact ætiology of pellagra is not yet known but that deficiency of niacin—actual deficiency in the diet deficiency relative to requirements or deficiency due to malabsorption—is the important factor that possibly another factor is associated with maize or other staple food substance and yet another with the patient s individual make up

Niacin requirements—The general opinion that 10 mgm of niacin is the minimum amount required daily is little more than a scientifically based guess The recommendation that a diet should contain 15 to 20 mgm is based on the above figure with a margin of safety

Niacin in food—Liver, lean meat yeast whole grain cereals peanuts and green leafy vegetables are the best source of niacin Milk eggs and white flour are a very poor source

Contributory factors—A point about which there can be no doubt is the effect of the sun in determining the dermal lesions both their seasonal incidence and their anatomical distribution It is suggested that the effect of the sun is purely a matter of trauma and that the skin in its ill nourished

state is particularly liable to damage or to put it another way the fullest effect of the morbid changes due to pellagra will fall on tissues already damaged by ultra violet radiation from the sun by infra red radiation from a fire or by friction of the clothes Other contributing factors are hard work, pregnancy, hypothyroidism (*vide supra*), and infections

PATHOLOGY

Niacin is an essential factor in the cellular enzyme systems diphos-

directly by niacin deficiency are described below —

The skin —The distribution and macroscopic appearance of the lesions are discussed below The changes are primarily inflammatory and then atrophic There is parakeratosis of the epithelial layer increase of pigment in the Malpighian layer followed by œdema and desquamation which leaves the surface red pigmented and rough The vessels of the dermis show hyaline degenerative changes

Nervous system —Demonstrable lesions are usually few, but they may be extensive in severe cases and involve the peripheral nerves cord and brain The lesions are by no means constant and different observers have described them in different systems the lesions described include demyelination or even complete Wallerian degeneration of the nerve fibres and chromatolytic degeneration of the cells of the Betz layer Clarke s column posterior root ganglia and anterior horn cells Subacute combined degeneration and atrophy of the cerebrum and cerebral œdema have been described Leptomeningitis has also been reported but the cerebrospinal fluid seldom shows any changes

Alimentary tract —The mucous membrane of the whole tract including the tongue and mouth shows hyperæmia and sometimes ulceration this is followed by atrophic changes in the mucosa and also wasting of the muscular coat

Other morbid changes —Death occurs usually from intercurrent disease so that the specific pathological picture is obscured However there is usually loss of subcutaneous fat and marked muscular wasting atrophy of the viscera including the heart and degenerative changes in the liver kidney and suprarenals both cortex and medulla

Blood picture —Some degree of anæmia is the rule it is usually of the microcytic type but may be macrocytic Leucopenia and relative lymphocytosis are common findings

Biochemical findings —In the urine there is a marked increase in urorosein a substance previously mistaken for coproporphyrin which disappears when successful treatment is given but this substance is also increased in many other conditions (Watson and Layne 1943)

There is usually achlorhydria or marked hypochlorhydria but Castle s intrinsic factor is present in the secretions

Normally the low limit of ... ie blood is about 0 600 mg per 100 c cm ... lower and in pellagrins distinctly lower ... the urine is normally about 5 mg per diem this is decreased in pellagra

PLATE XX (Pellagra)



Fig 1—Showing the characteristic skin lesions on the backs of the hands and forearms and under the breast.



Fig 2—Showing the separation of the pellagrous epidermis under treatment



Fig 3—Showing typical lesions on the back of the hands

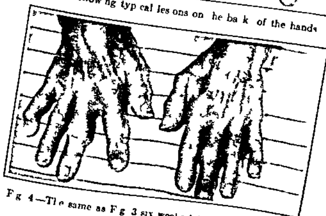


Fig 4—The same as Fig 3 six weeks later after treatment.

SYMPTOMATOLOGY

There is no accurate information about the incubation period, it is [illegible]

are commonly observed in children should be considered as pellagra

Onset.—The first symptoms to appear are variable, but *in any one* population they will usually be constant (suggesting that the pellagra syndrome, as it is usually seen, is due to a mixed deficiency) The most *characteristic symptom is the dermatitis*, and, being also a very striking one, it will be the symptom that will most frequently bring the patient under medical attention Careful inquiry will usually, however, elicit a *prior history of lassitude, loss of weight*, and gastro intestinal disturbances and soreness of the tongue and dysphagia In some cases there is definite mental deterioration before any other signs or symptoms appear The usual history is one of periods of improvement and then relapse over a period of several years before the full syndrome is developed, although there are instances in which the disease develops more rapidly It is noticeable that the onset and the relapses or exacerbations occur at one particular season of the year (*vide supra*)

A very large variety of signs and symptoms are attributed to pellagra but it is uncertain how many of these can readily be associated with the central syndrome and how many with other deficiencies The more specific signs and symptoms can be grouped under the following headings —

Dermatitis—The skin lesions, which are usually symmetrical at first suggest sunburn *There is hyperæmia and œdema*, and a burning or *itching* sensation The hyperæmia does not, however, clear up as it would in a true case of sunburn, but large scales form which may separate and leave a red rough area with a sharply demarcated pigmented edge In the acute stages, bullous eruptions may appear

The distribution of the skin lesions is typical in about 75 per cent of cases they appear on the backs of the hands other common areas are on the extensor surfaces of the forearms and arms on the dorsa of the feet (where these are exposed to the sunlight), on the shoulders, collarwise on the back of the neck (Casal's collar), and on the malar eminences (butter fly erythema) These are the areas that are most affected by sunburn

The dermatitis sometimes extends like a cuff around the wrists and ankles, here it tends to persist leaving a brownish stain on fair skins and sometimes *depigmentation on dark ones* *Other sites are the perineum* the elbows and the genital and axillary folds, especially when these areas are subjected to pressure of clothing Typical lesions are shown in Plate XX

The intestinal tract.—The attention to the mouth is first attracted by difficulty in taking hot and spicy foods The **tongue** is a scarlet red (*cf the more magenta or cyanotic tongue of riboflavin deficiency*) œdemato and indented and very sore to the touch, it then loses its epithelium takes on the characteristic glazed appearance There is a general infl matory condition of the whole mouth with aphthous ulcers along the and on the frenum of the tongue and ulceration of the gums wl often infected with Vincent's spirochæte There is increased saliva

to inability or disinclination to close the mouth over the swollen tongue The pharynx becomes involved in the same process this leads to difficulty in swallowing and disinclination to take food soon follows Later the tongue may become completely denuded of epithelium atrophied and fissured

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Nervous Tremors of the tongue and face muscles are noted early in the disease and the occurrence of Chvostek s sign (a spasm of the facial muscles on tapping) has been reported later this extends to other muscles There are fleeting pains in different parts of the body numbness and paræsthesias The deep reflexes are exaggerated at first later decreased and finally lost Peripheral neuropathy is often very troublesome, but recent work tends to suggest that this may be an associated condition (vitamin B_1 deficiency)

Later mental changes are characteristic symptoms of the disease there are headaches, sleeplessness dullness anxiety ...

So called toxic psychoses that develop after a febr...
oper...

Other signs and symptoms —The vaginal mucosa is usually red and sore and there may be a vaginal discharge There is nearly always progressive emaciation There may be irregular fever but it is not a constant symptom nor is it probably associated with the central pathological and symptomatic syndrome Anæmia is usually very noticeable this has been mentioned above

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

A typical case presents an unmistakable picture but the other end of the scale there are cases with slight and questionable symptoms that will defy accurate diagnosis except possibly by biochemical and therapeutic tests

Diagnosis will have to be considered under the following headings —

(a) **History** —Environment and diet general and special duration and seasonal variation of symptoms

(b) **Clinical picture** —Especially the characteristic dermatitis with glossitis diarrhœa and mental deterioration

(c) **Laboratory tests** —Decreased niacin in the urine and in the blood is the rule but the methods of estimating it are very complicated and certainly not within the scope of an ordinary diagnostic laboratory

(*d*) **The therapeutic test**.—This must be interpreted with reserve; all skin conditions are liable to improve by the administration of large doses of niacin, but the improvement will *not be so dramatic as is pellagra*. On the other hand, there are some cases that resist treatment with niacin; it should be given both orally and parenterally.

The skin condition has to be differentiated from sunburn, poison ivy dermatitis, trade dermatitis, lupus vulgaris, lupus erythematosis, erythema multiformis and syphilis; the gastro-intestinal symptoms from nutritional diarrhœas and sprue (in these there is usually, more commonly, a macrocytic anæmia, and less commonly achlorhydria, and in sprue there is fatty diarrhœa and a flat blood glucose curve on oral administration); and the nervous and mental symptoms from neurasthenia, beriberi, ergotism, lathyrism, tabes, Korsakoff's and Wernicke's syndromes and general paralysis of the insane.

PREVENTION

As pellagra is a dietetic disease, its prevention is primarily an economic and educational problem rather than a medical one. However, the *distribution of specific preventive substances at the worst period of the year* and the provision of early medical relief should form part of any anti-pellagra campaign.

Maize is only used as a staple diet because the people cannot get anything better, and provided it is suitably supplemented its consumption is not detrimental to health; the aim should therefore be the encouragement of suitable supplementation rather than the radical alteration of the diet.

Much can be done by **education and propaganda**. It is first necessary to make the people understand the necessity for including certain substances in their diet, and many will find the means for doing so, if not at first, perhaps at least in the course of a few years. Again, if they are made familiar with the signs and symptoms of the disease and are made to understand that it is amenable to treatment, and if treatment is put within their reach, they will probably present themselves for treatment in the earlier stages of the disease when its progress can be checked easily.

Naturally, methods of improving the **economic status** of pellagrous populations must be explored, but short of this it may be possible to encourage and even provide the means for home gardening or poultry keeping, and at the worst times of the year to distribute dried yeast or even tablets of niacin (100 mg. daily) through schools or other channel.

The best supplementary foods are fresh meat, especially pork, liver, whole grain cereals and green leafy vegetables. It may be necessary to fall back on tinned (canned) vegetables, *fish and meat which will serve* the same purpose but less effectively. The principle should be to increase the proportion of protein, as well as to provide an adequate amount of vitamin B complex.

In **institutions** or camps the disease should never arise if the diets are properly designed, but in the case of actual food shortages, when it may be necessary to fall back on some poorer staple substances such as maize, dried yeast should be provided.

Dried yeast, autolysed yeast or marmite (vegex) or some similar preparation is also a useful supplement for restricted **invalid diets**, when

for any reason it may be necessary to restrict other pellagra-preventing foods

TREATMENT

The treatment of pellagra seldom presents much difficulty, insofar as treatment of the individual moderately-advanced case is concerned, the real difficulty arises in the treatment of large poor populations and here the medical aspects are overshadowed by the economic ones Treatment can be considered under the four headings general, dietetic specific and symptomatic

General—The patient should be removed from the unsatisfactory conditions under which he is living, and put into hospital or at least to bed under good home-nursing conditions The room should be light and airy, but direct sunlight should be avoided until the patient's reactions to this have been ascertained Any concomitant infections such as ancylostomiasis or malaria, should be treated and any other dysfunctions, such as hypothyroidism and achlorhydria corrected or compensated

Dietetic—The patient should be given a good mixed high-protein diet, with a calorie value of at least 20 per cent above his normal requirements in which there is fresh meat (including liver or pork) whole-wheat (or other good cereal) meal leafy vegetables and fresh fruit

Specific—In most cases there will be immediate improvement following rest under good hygienic conditions with a good diet but if to this, suitable specific treatment is added, the improvement will be more rapid
in fraction of the vitamin B_2
It is best to give large doses—
three or four days and then
f 100 mg daily, until all signs
and symptoms have disappeared Niacin can also be given intramuscularly or intravenously in doses of 100 mg There are no disadvantages in the intramuscular method and it obviates the danger of non absorption, but not more than 10 mgm should be given intravenously by means of a serum syringe, and even this should be given slowly If the larger dose is considered necessary it should be given in a pint of 5 or 10 per cent glucose, slowly Large intravenous doses cause acute peripheral dilation that may be dangerous Niacinamide does not cause this dilation and may be given in the full therapeutic doses with impunity

The effect on the skin lesions is immediate and dramatic, the writer has seen an excellent case of pellagra entirely spoilt for teaching purposes, in a period of 48 hours by an ever enthusiastic house physician! But the improvement in the other symptoms may not be so marked It is very often advisable also to give riboflavin in cases of severe stomatitis and thiamin in cases complicated with peripheral neuropathy, and there are some cases in which liver extract also seems to be necessary, suggesting that this contains yet other specific substances There are some workers, who, in view of these facts, prefer to treat all cases of pellagra with liver extract parenterally and dried yeast by the mouth Further, there are some cases in which improvement is only slight and temporary with specific treatment unless this is combined with a general improvement in the diet and especially with an increase in the intake of good protein

Symptomatic—Drugs do not form an essential part of the treatment and in uncomplicated cases complete cure can be effected without them,

but sodium thiosulphate 7 grains daily, will help the **skin** condition, and arsenic in the form of Fowler's solution is recommended by some writers. The skin will improve more rapidly if the area is rubbed with olive oil. If there is a hypochromic **anæmia**, ferrous sulphate gr. iii, should be given three times a day.

Most of the gastro-intestinal symptoms will disappear on the administration of a suitable diet but, if **diarrhœa** persists, kaolin, bismuth or even opium should be tried in turn and, if constipation then supervenes, a mild vegetable purgative should be given for a night or two, and this should be followed by some bowel regulator, such as isapghul, every night.

The **stomatitis**, if it does not respond to riboflavin, should be treated with a mild antiseptic such as borax and glycerine, and if it is painful to the extent of interfering with the taking of proper nourishment cocaine may be added to the mouth application, 2 grains to the ounce. For the mental symptoms and sleeplessness sedatives such as bromides or luminal may be necessary.

PROGNOSIS

This will naturally vary with the circumstances. If the patient, even in an advanced stage, can be placed under ideal hygienic and dietetic conditions treatment is usually easy and in most cases will end in complete cure but there may be a relapse when the patient returns to his previous mode of life. The disease, however, usually occurs amongst poor populations where the intensity of the symptoms will vary according to the degree of the dietary deficiency, and the usual history is that of improvement during the cold months of the year (in sub-tropical climates) with progressively more severe relapses during the summer months of each year.

In a small percentage of cases the patient appears to resist all forms of treatment and after short temporary remissions deteriorates rapidly and eventually dies of some complications.

The death rate in Italy is given as 3 to 5 per cent, and in the United States as about 10 per cent, but in some outbreaks in the latter country, it has been placed as high as 30 per cent.

In alcoholics, in chronic malarial and dysenteric subjects, and in any febrile state the prognosis is less favourable.

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SCURVY

Definition.—Scurvy is a dietary-deficiency disease characterized by spongy and bleeding gums and superficial and deep hæmorrhages in different organs and tissues of the body, which if unchecked ends fatally; it is caused by the deficiency of vitamin C (ascorbic acid) in the diet and prevented or cured when it has already developed by the taking of citrus fruits or of other fruits or vegetables containing a sufficiency of this vitamin.*

Historical.—Scurvy was the first dietary-deficiency disease recognized as such; its cause was known at least three hundreds years before the word 'vitamin' was invented. There is little evidence that the disease was known to the early Greek or Indian medical writers and it seems to have made its debut in the fifteenth century when long voyages of discovery became fashionable. In 1564 Ronsseus, a Dutch physician, described scurvy and its treatment by means of oranges, but did not suggest that lack of them was the cause of the disease. However from this time onwards the practice of carrying fruit and vegetables and even growing the latter on ships to prevent scurvy began to be adopted. In 1747 James Lind carried out his classical experiments which showed that the juice of oranges and lemons prevented the development of scurvy, and Captain Cook in his voyages of

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*The status of scurvy as a tropical disease might well be questioned in view of the fact that several arctic and antarctic expeditions have been marred by its occurrence amongst the personnel; nevertheless the inclusion of a short chapter on this disease can be justified on the grounds that, whereas the average practitioner in the temperate countries of Europe or America will seldom encounter a case of frank scurvy, except possibly in the form of Barlow's disease (infantile scurvy), his opposite number in the tropics may well see a large number of such cases.

but sodium thiosulphate, 7 grains daily, will help the **skin** condition, and arsenic in the form of Fowler's solution is recommended by some writers. The skin will improve more rapidly if the area is rubbed with olive oil. If there is a hypochromic **anæmia**, ferrous sulphate, gr. ii, should be given three times a day.

Most of the gastro-intestinal symptoms will disappear on the administration of a suitable diet but, if **diarrhœa** persists, kaolin, bismuth or even opium should be tried in turn and, if constipation then supervenes, a mild vegetable purgative should be given for a night or two, and this should be followed by some bowel regulator, such as isapghul, every night.

The **stomatitis**, if it does not respond to riboflavin, should be treated with a mild antiseptic such as borax and glycerine, and, if it is painful to the extent of interfering with the taking of proper nourishment, cocaine may be added to the mouth application, 2 grains to the ounce. For the mental symptoms and sleeplessness, sedatives such as bromides or luminal may be necessary.

PROGNOSIS

This will naturally vary with the circumstances. If the patient, even in an advanced stage, can be placed under ideal hygienic and dietetic conditions, treatment is usually easy and in most cases will end in complete cure, but there may be a relapse when the patient returns to his previous mode of life. The disease, however, usually occurs amongst poor populations where the intensity of the symptoms will vary according to the degree of the dietary deficiency, and the usual history is that of improvement during the cold months of the year (in sub-tropical climates) with progressively more severe relapses during the summer months of each year.

In a small percentage of cases, the patient appears to resist all forms of treatment and after short temporary remissions deteriorates rapidly and eventually dies of some complications.

The death rate in Italy is given as 3 to 5 per cent, and in the United States as about 10 per cent, but in some outbreaks in the latter country, it has been placed as high as 30 per cent.

In alcoholics, in chronic malarial and dysenteric subjects, and in any febrile state the prognosis is less favourable.

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[illegible]

Ascorbic acid is very labile and is very likely to be destroyed by [illegible]

canned fruit, less than 30 per cent of the original content of ascorbic acid is preserved, but modern canning methods retain much more than this Again, during storage, of potatoes for example, the ascorbic acid is quickly lost

Milk is not a good source of ascorbic acid, but, if the cow is fed on fresh grass, her milk will contain far more than if she is stall-fed Most pasteurized milk supplied in cities is a negligible source of vitamin C Human milk is a much better source than cow's milk

When fresh fruit and vegetables are hard to obtain, ascorbic acid can be supplied by sprouting pulses or cereals, unmilled grain is of course necessary The following method of preparing sprouted grain is given by Aykroyd (1941) —

Grains, such as dâl, gram or wheat, or legumes, particularly unsplit peas, are first soaked in water for 24 hours and are then spread out on damp earth or on a damp blanket and covered over with a moist cloth or sack (gunny bag) which is kept moist by sprinkling water upon it from time to time After two or three days the grains will have sprouted and be ready for use The sprouted grains should be eaten raw or after cooking for not more than 10 minutes

PATHOLOGY

The deficiency of vitamin C causes an imperfect formation of connective tissue, with failure to develop true supporting tissue, there is not proper adhesion between the cells of the epithelium of the capillary walls, so that these rupture very easily on the slightest trauma or when the internal pressure is increased, and similarly scar tissue does not form properly and is very weak Osteoblasts fail to differentiate, and there is def [illegible]
bla [illegible]
dev [illegible]
are [illegible]
by 'amyloid' connective tissue

The post-mortem picture will be largely influenced by the secondary deficiencies and the superimposed infections, but a constant finding will be numerous hæmorrhages in most of the tissues and organs, including the brain

[illegible] —A microcytic hypochromic anæmia, that responds read- [illegible] of vitamin C, has been reported, but the writer [illegible] any anæmia as due to ascorbic-acid defi-

discovery (1772 75) ... the principle into practice ... striking result for ... whole ... earlier

by Holst and Frolich ... and later given the ... Szent Gyorgyi (1933) ... synthesized by Reich ...

stein Haworth and others

EPIDEMIOLOGY

... (*vide supra*) ever since ... the shorter duration of ... ilors It still occurs in ... ife amongst the British and Indian troops in Iraq during the 1914–18 war It is very liable to occur in Indian African or Chinese labour forces working in unfamiliar surroundings as *the uneducated labourers are often very conservative* and do not eat the unfamiliar local fruits and vegetables It appears to be the most common specific deficiency associated with famines it occurred in India during the *Hissar famine in 1940* (*Nicol 1940*)

Sporadic cases not infrequently occur amongst invalids kept on a milk diet and in the form of Barlow s disease amongst infants fed on boiled or preserved milk or on the milk of stall fed cattle without the supplementation of fruit juice or fresh vegetables

The disease has no geographical or seasonal limitations and it may occur amongst persons of every race both sexes and all ages In certain special circumstances it may exhibit a seasonal incidence just as it may *appear to attack certain groups in a population but the incidence is always* explainable in terms of vitamin C intake

ÆTIOLOGY

Scurvy appears to be a simple vitamin deficiency disease

Ascorbic acid which man and other primates and certain other animals notably the guinea pig are unable to synthesize is an essential element for cell metabolism it must therefore be taken in the food or the *organism will suffer* In health the tissues are saturated with this vitamin so that it takes about six months of deficiency before the signs and symptoms of frank scurvy appear A sub scurvy state is now recognized *evidence of which can* sometimes be elicited prior to the onset of frank scurvy

The daily requirements of ascorbic acid are 70 to 100 milligrammes for the adult although 30 milligrammes will prevent the development of scurvy Children require relatively more as also do pregnant and lactating women and persons suffering from fever malaria in particular appears to exhaust the ascorbic acid reserves rapidly

Sources of ascorbic acid—The classical and probably the most convenient sources of vitamin C are citrous fruits especially oranges and lemons the juice of which contains an average of 60 mg of ascorbic acid per 100 grammes Other fruits rich in vitamin C are black currants (200 mg) strawberries (50 mg) cape gooseberries (50 mg) pineapples (60 mg) guavas (300 mg) papayas (40 mg) and tomatoes (30 mg) Fresh leafy vegetables roots and tubers also contain large amounts provided that they are fresh and either uncooked or carefully cooked notably

Of the laboratory tests the estimation of the urinary excretion of ascorbic acid is the simplest On a minimum adequate intake of 25 mg, the daily excretion is about 13 mg there is a sharp response to a test dose of 700 mg if the subject is saturated but if not it may be several days before there is evidence of an overflow in the urine The urinary ascorbic acid falls to *nil* in frank scurvy, and no appreciable amount is excreted until at least one gramme of ascorbic acid has been given

The estimation of the blood ascorbic acid is also relatively simple If this is as high as 0 7 milligrammes per 100 c cm, it may be assumed that the patient is saturated A low value does not, however necessarily mean that there is ascorbic acid deficiency

In differential diagnosis, most of the hæmorrhagic diseases will have to be considered, and it may be necessary to make a platelet count and do a prothrombin test

PREVENTION

The prevention of scurvy has been practised on ships of the navies and merchant services of many nations for several hundred years often by regulations that make it compulsory to carry fresh fruit or fruit juice for consumption by the crew In institutions and armies it can be prevented by including in the rations some good source of vitamin C and by training cooks not to destroy such of the vitamin as is present in raw food by overcooking it, or by using copper or brass utensils When all other sources are precluded it can be provided by sprouting grain (*vide supra*)

The present shortage of shipping has reduced the amount of citrous fruit that can be imported into Great Britain To replace this deficiency, synthetic vitamin C is being used freely

Education and propaganda play an important part in prevention the importance of taking fresh fruit and vegetables or sprouted grain should be impressed on school children and pregnant women in particular the latter for their own benefit and for that of their infants

As a general rule, the prevention of scurvy is not so much an economic problem as is the prevention of pellagra or even beriberi but this aspect will arise in the case of famines During the Hissar famine in 1940 pow- [illegible]

Infants on artificial food or on pasteurized milk should always be given fresh fruit juice daily, this will also apply to infants whose mothers are on a low ascorbic-acid intake and in fact it will be a safe precaution to apply to all infants, as well as to invalids on a milk diet

TREATMENT

This presents no difficulties if fruit juice or synthetic ascorbic acid is available Doses up to 700 mg of *l*-ascorbic acid should be given by mouth daily [illegible] In [illegible] ain- [illegible] until [illegible] scer- [illegible] this

ciency and recent experimental work has failed to establish the earlier claims

SYMPTOMATOLOGY

Latent period —In infants 'Barlow s disease' usually develops between the sixth and the eighteenth month and similarly in a well saturated adult it is about six months before there is any *clinical evidence of the deficiency* although in a case in which a partial deficiency has existed for some time the disease may be precipitated within a shorter period

Onset —The first signs are pallor breathlessness *anorexia and general* weakness this is followed by sponginess and bleeding of the gums then swelling so that they almost envelope the teeth which become loose

Progress —Large ecchymoses may appear in the skin then sub periosteal *hæmorrhages* and there may be hæmorrhages into the joints and other serous cavities or even into the brain There may be hæmoptysis

Ieanwhile severe anæmia may
blood but also it is claimed
come secondarily infected so
h drop out and usually the
patient becomes progressively weaker and eventually dies of some complication such as pneumonia

In infants the most striking additional feature is the extreme tenderness of the joints so that the infant is terrified when anyone approaches its cot If the knee is flexed and everted a swelling of the lower end of the femur will be seen which is usually symmetrical this is not tender Later the upper limbs may be similarly affected There is also usually radiological evidence *e g* sub epiphysial hæmorrhage or cessation of the development *The spongy gums and other signs will also be present*

DIAGNOSIS

This can be made on (a) *the dietetic history* (b) *the clinical examination* (c) the therapeutic test and/or (d) certain clinical and laboratory tests

Frank scurvy will usually present little difficulty from a clinical point of view if there is a dietary history that is compatible with vitamin C deficiency However it is unwise to diagnose scurvy in an adult on a mixed diet or in a breast fed child on clinical examination alone in such
osis by *laboratory tests or at least the*
A good clinical response within a few
of ascorbic acid constitutes a positive
also be accepted

A relatively simple clinical test is Gothlin s capillary fragility test a sphygmomanometer band is placed on the arm and the pressure raised to 90 mm of mercury for three minutes the arm below the band is then inspected with a hand lens and in cases of deficiency *there will be numerous* capillary hæmorrhages No clinical test is however entirely reliable although this is better than Rotter s intra dermal test that most reliable workers have now discarded

EPIDEMIC DROPSY*

Definition—Epidemic dropsy is the provisional (and not very appropriate) name given to a non-infectious disease which is characterized by gastro intestinal disturbances œdema of the extremities certain specific skin manifestations and cardiac dysfunction, and is frequently fatal, it has a very limited geographical and racial distribution being confined mainly to Bengal and Bengalees, and its exact ætiology is as yet unknown, but it is undoubtedly associated with food and probably with mustard oil

Discussion—This disease has in the past suffered many things of many theorists It has been fitted into a variety of categories to which it quite obviously does not belong by both local and long-distance investigators who have exalted

*The [illegible] ritten with the aid of some notes [illegible] Chaudhuri his late colleague and [illegible] cutta whose clinical experience of

is not usually necessary Infants require 40 mg daily for two or three weeks When synthetic ascorbic acid is used, it is good practice to supply a natural source of vitamin C in the diet as well, since cases have been reported in which the response to the synthetic vitamin alone was not satisfactory

Subsidiary treatment is seldom necessary, but the correction of this deficiency may uncover other deficiencies so that a diet rich in all important vitamins should be given whenever possible

If the specific treatment is given, even in advanced cases, the **prognosis** is usually good

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* The clinical paragraphs of this paper were written with the aid of some notes given to the writer for this purpose by Dr R N Chaudhuri his late colleague and the assistant professor of tropical medicine in Calcutta whose clinical experience of this disease ante-dates the writer's by several years

casual clinical observations of secondary importance—both in this disease and in the diseases to which they have attempted to liken it—to the position of main symptoms and have then in these distorted pictures seen similarities which do not exist in the typical pictures of these two diseases

The two diseases with
dropsy Epidemic dropsy
diet of which (admittedly)
short latent period, betwe
beriberi the writer can see
the 'wet form of beriberi the similarities are more apparent than real, and
between epidemic dro
tors have seen any si

Epidemic dropsy
dietetic diseases and
unique pathology, an
fore deserves conside
that is at present on
population of about
of its study seem to

EPIDEMIOLOGY

Geographical distribution—Epidemic dropsy was first reported in Calcutta in 1877 and this city has been the focal centre of this disease ever since *This is primarily because Calcutta is a large town with a very large Bengalee population and because medical and popular attention has been drawn to the disease here* It was reported in Mauritius in 1879 amongst labourers from Calcutta (who probably brought their own food with them or at any rate lived on the food to which they were accustomed, imported from Calcutta), and more recently an outbreak has occurred in Fiji, again amongst labourers imported from Bengal It frequently occurs in other centres in Bengal and in the neighbouring provinces, Assam, Bihar, and Orissa, and to a less extent in the Central and United Provinces

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been

Epidemic status—Sporadic cases are seldom seen The disease occurs in small or large outbreaks, involving one family or a large group, *e g* a students' mess or some institution Several outbreaks will occur at the time, giving the semblance of an epidemic, but such outbreaks will be scattered widely in the locality, and it will usually be impossible to trace any link between any two of them When the disease occurs in a *labour force, it will occur amongst certain groups that feed together*

It is a disease of middle-class Bengal families, the entire family, except the infants and young children, is usually affected in varying degrees of severity, and the servants, of which there may be several in a large Hindu joint-family, are usually also involved although they may escape if they have separate feeding arrangements

Age, sex, race, and economic status—Suckling infants are never affected and young children up to the age of four years very seldom, the sexes are equally susceptible, as noted above Bengalees are particularly affected although the disease also occurs amongst Anglo Indians, *and* others who eat both rice and mustard oil, but it is practically unknown amongst Europeans and Marwaris in Calcutta neither of which communities use rice as their staple diet, nor mustard oil in cooking and the poor-

est classes of the community usually escape (These people often cannot afford mustard oil and also they do not throw away their rice water)

ÆTIOLOGY

During the last sixty years, many theories have been formulated, they have lived their days, become history, and have been revived again

The **theories** that have been put forward can be grouped as follows —

(*a*) That it is caused by an infecting organism a bacterium or a virus, that can be passed from person to person,

(*b*) That it is an intoxication acquired from

(*i*) diseased rice
(*ii*) mustard oil or
(*iii*) some other source,

(*c*) That it is a food-deficiency disease

(*a*) Whilst the ... s from time to time, epidemiological and the mode of origin

(*b*) Similarly the **food-deficiency theory** will not stand at least not alone, most of the main epidemiological facts are opposed to it However, people who take milled rice as their staple diet even if this is parboiled, are not living very far above vitamin B_1 deficiency line, so that this cannot be entirely dismissed as a possible contributing factor

(*c*) We are thus left with the **intoxication theory** (*i*) Rice has al- ... it is natural that it should as all ... communities Acton and Chopra ... It was suggested that after parboiling and milling, if the rice were allowed to get damp in transit, and/or was kept in a damp and airless *godoun* (store-room), it was likely to become infected by a gram positive spore-forming bacillus, which, causing degenerative changes in the starch of the rice, produced a central opacity in the rice grain that could be seen easily when this was immersed in water This degenerat... water-soluble toxin th... e wide-spread capillary ... lus was found in some s... btain a histamin like substance from other samples but there were many gaps both on the bacteriological and on the pharmacological side, particularly in the matter of controls in this attractive theory and as such it was received with considerable scepticism

Although the broad epidemiological observations, for example that the disease was virtually confined to rice eating people, were in favour of any *rice theory, and sometimes amateur local enquiries seemed to suggest* that certain supplies of so-called 'diseased' rice might be responsible for some of the outbreaks, no expert epidemiological investigation has been carried out prior to 1935 Discussing the problem in an editorial in the *Indian Medical Gazette* of December 1935 the present writer commented —

'The epidemiological investigations must be raised from the anecdotal to the scientific level The population subjected to enquiries must be a large one and only selected on a geographical, not on an economic social or religious basis, the enquiries must be made amongst those who have not as well as those who

have suffered from the disease, the mild cases of the disease must also be taken into account, and this presents difficulties as it means that a careful medical *examination of the whole population at the time of the outbreak* is necessary, histories taken at a later date may be misleading. Very few investigations of this nature have been undertaken but it is only through such investigations that we are likely to reach a solution of the problem'

Recent work.—An epidemiological investigation was undertaken by Dr R B Lal, the professor of epidemiology and vital statistics at the All-India Institute of Hygiene, Calcutta, and his staff, in six different areas, in Bengal, Bihar, and Assam, including a tea-estate, where an outbreak of the disease had been recognized and reported by Dr Charles Terrell These investigations appeared to point once more to mustard oil as the probable vehicle of the noxious factor, and the same workers, in an investigation conducted with the clinical collaboration of members of the staff of the Calcutta School of Medicine, were able to produce suggestive symptoms in volunteers fed on samples of mustard oil that had come under suspicion in epidemic dropsy outbreaks (Lal *et al* 1937–41)

During the last half century mustard oil has been suspected repeatedly but in 1926 Sarkar recorded an outbreak in which several patients had all the symptoms of severe epidemic dropsy after taking oil that had been contaminated with argemone oil (from the seeds of *Argemone mexicana* local names *sialkata* or *katakar* oil) In 1928 Kamath, reporting an outbreak in which mustard oil was taken and applying his data to support the infection theory, noted that oil from a seed, known locally as *odissimari*, was also used, this seed has now been identified as *Argemone mexicana*

Attention was thus directed to a specific contaminant of mustard oil and feeding experiments were carried out at the Calcutta School of Tropical Medicine on human volunteers and on animals (Chopra, *et al*, 1939) with very suggestive results

We have now arrived at the position in which mustard oil has been incriminated once more, but on this occasion the case against it rests on a much sounder basi ... ntal evidence Argemone oil, a common ... en shown to produce symptoms identical ... whether it is administered accidentally ... a number of recent outbreaks, it has been found that the mustard oil used by the victims was badly contaminated with argemone oil and that when its use was discontinued the outbreak subsided

We know that argemone oil contains a noxious agent, but up to the present time chemists and pharmacologists are not agreed as to its exact nature, or how it acts, whether it is an independent poison that produces its ill effects, grain for grain according to the dose in which it is taken, or whether the substratum is an important factor and the degree of toxicity depends on the excess of one food substance in the diet or on the absence of another

Argemone oil is not an adulterant in the sense that it is often added to the oil by the retailer, deliberately for the sake of increasing his profit, but it is an accidental contaminant of the mustard crop as it grows in the field, it is a self-sown weed which can be distinguished easily from the mustard plant when the crop is harvested, and although the seeds are very similar, they could be picked out by a careful farmer

It is quite understandable that some years would be more favourable to the weed than others and that its percentage incidence in the crop will

vary from place to place, but apparently it is a very common contaminant and a large number of samples of oil show its presence, so that it is easier to account for the wide prevalence of the disease than it is to understand why it is not more prevalent It is for example not quite clear why epidemic dropsy is comparatively rare amongst the poorer Anglo Indian community who use mustard oil for cooking almost exclusively Does it depend on the amount of argemone oil present? Lal and his coworkers (1941) place the maximum safe amount at 0 5 per cent Is it simply because it is heated and partly inactivated or is it something to do with the general composition of their diet in which rice does not preponderate to the extent that it does in most Bengalee diets?

There has long been a strong belief prevalent amongst both patients and doctors that rice *per se* is bad for an epidemic dropsy patient this belief is independent of the rice-toxin theory because it applies to any form of rice sound or diseased Dr Ellis C Wilson studying cases in the hospital of the Calcutta School of Tropical Medicine noted that there was a distinct increase in the œdema whenever an epidemic dropsy patient was given a rice diet There is therefore some evidence that people who live on a diet consisting largely of rice possibly by virtue of its high carbohydrate/vitamin B ratio are more susceptible to the disease and that rice though not the main culprit or the vehicle of the noxious factor does play a part in the ætiology of epidemic dropsy

In the study of vitamins the idea of conditioned toxicity is now gaining ground there are numerous examples reported of the toxic effect of a toxic substance being conditioned by the nature of the diet and/or the state of vitamin saturation of the subject *e g* selenium poisoning and a high protein diet lead poisoning and vitamin C and indol and vitamin B Is this possibly another such example? Such an hypothesis would provide a means of co ordinating some of the earlier theories regarding epidemic dropsy with the latest one, for specific food deficiency was visualized as a possible cause long before the present vitamin age

Both the clinical and the pathological evidence (*vide infra*) support the epidemiological and experimental evidence and indicate that the disease is far more likely to be due to an intoxication than to either an infection or a vitamin or other food-deficiency

To **summarize,** epidemic dropsy is apparently caused by the consumption of some toxic substance in mustard oil probably a constituent of argemone oil, a common contaminant of mustard oil the effect of this toxin is enhanced if the diet is predominately a rice one

PATHOLOGY

The characteristic pathological change is a persistent dilation of the smaller blood vessels not simply of the capillaries in all the layers of the skin in the heart muscle, and in other organs and tissues associated with slight perivascular infiltration by large mononuclear cells increased permeability, and local œdema The toxin appears to have a direct specific action on small blood ves els

These changes can be seen in all the layers of the **skin,** and in the subpapillary plexus there is often new vascular formation which may progress to the development of hæmangiomatous condition that gives rise to the so called 'sarcoids' There is often increased pigmentation in the basal layer, and some pigment will be seen in the deeper layers of the skin

There is œdema in the corium, where the collegen fibres may be swollen, and in the subcutaneous tissue The 'sarcoid' is a vascular tumour, with few connective tissue cells, no fibroblasts and no inflammatory cell exudate, covered by a flattened epidermis which shows thickening and down growth deep into the normal corium at the edge of the tumour

In the **heart,** there is marked vascular dilation between the muscle fibres so much so that sections sometimes give the appearance of free extravasations of blood that have dissected out individual muscle fibres or bunches of fibres

In the ***eyes,*** *there is great engorgement of the uvea which results in* over production of aqueous humour, increased tension in the anterior chamber, and glaucoma

The blood picture—There is usually a distinct normocytic orthochromic anæmia which is apparently due to depressed hæmopoietic function (Napier and Sen Gupta 1940) The leucocyte count is usually slightly raised and there is a shift to the left in the Arneth count The erythrocyte sedimentation rate is increased considerably

The **urine** shows no constant changes, there is however frequently a trace of albumin

SYMPTOMATOLOGY

The **latent period** between the consumption of the noxious material and the onset of the first symptoms (this can sometimes be estimated with a fair degree of certainty but of course at other times not) is very variable *from two or three days to two or three weeks It is probably depend*ent on the dose taken Similarly the **onset** may be sudden or insidious, again this probably depends on the same circumstances It is usually possible to obtain a history of nausea, loss of appetite, and looseness of the bowels for a few days, with this there may have been irregular fever but there is seldom much fever by the time the patient reaches the hospital though the diarrhœa often persists

In the acute cases breathlessness on the slightest exertion, swelling of the feet which is much worse towards the end of the day, and in some outbreaks skin manifestations will develop rapidly The pulse rate is usually rapid and may be very irregular the blood pressure is variable In very severe cases, the heart condition progresses rapidly and the patient, now confined to bed, is orthopnœic, or he may die suddenly before the full seriousness is appreciated short
ness of breath will persist as e diet
but will subside rapidly unde *mia of*
the skin may subside, leaving the sarcoids

Finally all the more acute manifestations subside and as long as the patient remains in bed, he feels perfectly well but he may be left with a weakened myocardium which prevents him from returning to full work for many months There are, however amongst better class patients many whose cardiac condition appears to be normal, but in whom a cardiac neurosis *develops that is even* harder to cure than any true cardiac dysfunction

Some of the symptoms will be considered in a little more detail

The **œdema,** which is both central and peripheral in origin, is an almost constant symptom but variable in degree and very rarely general anasarca develops

The **cutaneous manifestations** are [illegible] in some epidemics and apparently rare in others. In 1934 [illegible] the School of Tropical Medicine, 15 [illegible], and since special attention has been drawn to them, they appear to [illegible] than they were hitherto. They include a [illegible] vascular mottling of the skin, hyperpigmentation [illegible] particularly the face, a petechial rash, and the [illegible]

The "**sarcoid**" [illegible] to Boeck's benign sarcoid and [illegible] mitted—a "fleshy" tumour [illegible] the size of a pin's head to that of a [illegible] culated. It is easily injured and is liable [illegible] to suppurate.

The heart.—This is frequently enlarged. A [illegible] due to relative mitral incompetence and an [illegible] sound, due to compression of the [illegible] are common, and there may be a pulmonary systolic murmur due to dilatation [illegible] In severe cases there are signs of congestive cardiac [illegible]

The electrocardiogram commonly [illegible] tachycardia of sinus origin and extra-systoles are not [illegible] the P-R interval has been found to be abnormally [illegible] in a large percentage of the cases investigated, and an abnormal T wave and auricular fibrillation have been found. Orthodiagrams frequently show that the heart is enlarged especially the left ventricle and the right auricle.

Other symptoms.—Patients often complain [illegible] burning or a pricking sensation and of vague pains all over the body, but [illegible] of definite "neuritic" paralyses, or areas of anaesthesia. The [illegible] sometimes appear to be brisk at first and later poor or even [illegible] in most cases there is little deviation from normal in any reflexes. [illegible] these symptoms may of course be due to associated vitamin deficiency.

Glaucoma develops in about 5 per cent of cases. There is early complaint of rainbow haloes around a light, dimness of vision, then progressive contraction of the visual field and, if unrelieved, eventually complete blindness. There is usually little pain, but on examination the increase in tension will be obvious.

Abortion is the rule in pregnant women.

DIAGNOSIS

This is based on the clinical picture and the dietetic history. If several members of a family give a history of acute diarrhoea followed by oedema of the legs, with or without flushing, which is warm to the touch, and shortness of breath on exertion, careful enquiries should be made regarding the diet of the family, and other members should be examined and questioned for minor signs of the disease.

The characteristic oedema and erythema is not matched in any other condition, nor are the so-called sarcoids, though these are somewhat like the eruption in verruga peruana (another local disease that occurs curiously enough on almost exactly the opposite side of the globe). The disease has [illegible] h there is sw[illegible] mass, and ca[illegible] ment here, in [illegible] Between

epidemic dropsy and the 'dry' form of beriberi with its gradual onset, wasting and weakness, and *pronounced* neuropathies, there are no points of similarity to be discussed In the 'wet' form, the latent period is again longer than that of epidemic dropsy, the œdema often disguises underlying wasting and neuropathies, and is 'cold', that is unaccompanied by hyperæmia there are no other cutaneous manifestations, and in the heart condition there is very frequently a dramatic response to the administration of thiamin chloride All these points taken together will usually make is easy to distinguish even isolated cases, and, when there is a group of cases should make confusion impossible

PREVENTION

It is obvious that this will depend on the final verdict on the cause of the disease, but the present state of our knowledge certainly justifies the adoption of public health measures aimed at the prevention of the contamination of mustard oil by argemone oil, even as an experimental measure

Preventive measures must be started with the agriculturist to whom the danger of weed should be poir bear on him indire and condemning a ge of seeds of *Argemone mexicana*, or even by testing the oil that is supplied to the retailer But there are technical difficulties about the latter procedure as the nitric acid test*, which has up to now been relied upon for detecting contamination, is not entirely specific

An interesting observation was made by Terrell (personal communication) namely that in some northerly districts of Assam the mustard and the *Argemone mexicana* do not ripen coincidentally, so that the latter seed is not harvested in these districts, the mustard oil is never contaminated, and epidemic dropsy does not occur

As far as the individual is concerned the only advice one can give is to warn him to buy his oil from a safe source and/or to have it tested

TREATMENT

This is essentially symptomatic and dietetic no specific is known

Rest is the first essential, even if the cardiac symptoms are not prominent as, until the patient has been placed on his new dietary regime for

of returning

The **diet** will depend on the symptoms to some extent, but, if there are no contra indications, a well-balanced diet containing at least the full quota of protein and from which rice and mustard oil are excluded, should be given Bread or *chappatis* should be given in the place of rice If the diarrhœa persists this may be stopped by placing the patient on milk or even limewhey and albumin water may be necessary for a few days, but

* About 10 c cm of the oil is shaken up with an equal quantity of colourless nitric acid after two minutes a yellow or reddish brown layer appears at the bottom of the test tube The test is reported to be roughly quantitative and to detect about 1 per cent of argemone oil

care must be taken not to keep up this restricted dietary for too long and if there is much œdema, so much fluid may be contra indicated In the latter case salt also should be restricted

Drugs —An initial purgation with two drachms of liquorice powder at night followed by two or three days of castor oil emulsion (a drachm to the ounce), or one drachm of sodium sulphate, every two hours for the first day and every four hours for the next two days will help to control the diarrhœa and to some extent the œdema but if after this the former persists bismuth and opium should be substituted

A mixture containing tincture of ephedra 20 to 30 minims and 10 to 15 grains of calcium lactate thrice daily, is prescribed as a routine procedure at the Calcutta School of Tropical Medicine theoretically because ephedrine is vaso constrictor and a circulatory stimulant at least patients appear to do well on it A diuretic *e g* diuretin grs 10 is added if there is any œdema If the œdema is more extensive ammonium chloride grs 10 is given three times a day and then an injection of one of the mercurial diuretics such as neptal or mersalyl For congestive heart failure digitalis in adequate doses should be given and in severe cases venesection may be advisable

Complications must be treated as they arise the fluid may have to be removed from serous cavities Glaucoma must be watched carefully and if there is no improvement with general treatment and the visual fields tend to diminish, trephining or anterior sclerotomy may be necessary

PROGNOSIS

Even in the mild case the patient is not really fit for manual work within three to four weeks in the moderately severe case with any evidence of cardiac involvement he will not be fit to resume even clerical work within this period and, in the severe case the patient will be incapacitated for several months

The death rate in an outbreak will usually be about 5 per cent but in some severely affected families half the members have died Death is from heart failure

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LATHYRISM

Definition—Lathyrism is a syndrome of which the most prominent clinical feature is muscular weakness and later spastic paraplegia it occurs *especially during times of drought and famine* amongst certain population groups whose staple diet is a vetch *Lathyrus* in India Spain and elsewhere

Historical—The condition was recognized as a dietetic disease by the early Indian medical writers and later by Hippocrates In the 17th century it was definitely associated with the eating of the vetch *Lathyrus* from which it derived its name and in some European countries edicts were proclaimed forbidding its use In India *the condition was reported early in the last century by several British* physicians and since then outbreaks have occurred frequently

EPIDEMIOLOGY

The disease has appeared in several European continental countries including France Italy, and Spain (in Barcelona Cuenca Ciudad Real Toledo Valladolid and Madrid provinces) in North Africa Abyssinia Iran and in India (the Central and United Provinces Central Indian States and Bihar in particular) In North Rewah (Central India) in 1921 it was estimated that 6 per cent of the total population of about a million people were affected There have been a number of recent reports of the condition in Spain (Jimenez Diaz *et al* 1943 and Martinez Almeida 1943)

The persons most affected are males between the ages of 15 and 30 that is during the most active period of their lives

It is a disease of famine years and it occurs almost exclusively amongst members of the lowest economic classes but the individuals affected are often well nourished since the vetch provides a diet of high caloric value

ÆTIOLOGY

The actual cause of the disease is still in doubt It is not a pure defic [illegible]
with [illegible]
and [illegible]
the [illegible]
dal is incriminated but in other countries *L cicera* and *L clymenum* are the common vetches used

On the other hand, it is almost certainly not a pure food intoxication for the vetch is used by many people as a staple diet and by a much wider group as an additional item in the diet without causing any of the symptoms of lathyrism

There seem to be three possibilities

(*a*) That it is caused by toxins derived from *Lathyrus sativa* which has been grown under certain special conditions or which has undergone certain changes after harvesting through having been kept in damp storage for example

(*b*) That it is due to contamination of the *Lathyrus* crop by some other vetch *e g Vicia sativa*, locally known as *akta* that is not easily distinguished from *Lathyrus sativa* and which either normally or under special circumstances is toxic

(*c*) That the disease is a conditioned toxicity that is to say the pathological changes are caused by a toxin in *Lathyrus* or less probably in some common contaminant of the *Lathyrus* crop in the absence of some vitamin or other food factor that normally neutralizes its effect This has *for some time been the present writer's interpretation of some of the* apparently contradictory observations regarding the ætiology of this disease in India, the recent work of Jimenez Diaz and others (1943) in Spain seems to provide considerable support for this hypothesis

Toxins were isolated from the germinating *Lathyrus sativa* by Acton and Chopra (1922) and from *Vicia sativa* var *angustifolia* Howard Simonsen and Anderson (1922) have isolated a toxic base divicine which has the properties of [illegible] tral nervous system in ex [illegible] experimental evidence in [illegible] e other the contaminating [illegible]

By feeding monkeys on pure samples of lathyrus peas Stockman (1929) in Glasgow produced a temporary spastic paralysis that was very similar to the more permanent condition lathyrism observed in man Geiger Steenbock and Parsons (1933) prod [illegible] and bone [illegible] nges in rats by feeding t [illegible] r diet on the seeds of L [illegible] ts the higher the per c [illegible] as not prevented but n [illegible]

Lewis and Esterer (1943) produced a similar condition in rats by the cold water extract of the sweet pea

Jimenez D [illegible] ncluded that the condition is due to ea [illegible] to the exclusion of other dietary substa [illegible] with the lipoid fraction and that there [illegible] tance that if taken in sufficient amount will antagonize the vetch toxin This antagonistic substance is not a vitamin and can apparently be synthesized by some animals (but not by man or the horse) and is present in most food of animal origin

The horse is apparently the only other mammal commonly affected in nature

taking the body-weight in the hands and balls of the feet and shuffling the buttock forward

PREVENTION AND TREATMENT

All measures to discourage the use of *Lathyrus* as a staple diet should be taken These will amount to anti famine measures by irrigation schemes and by a better distribution of other staple foods during periods of drought for example Much has been achieved on these lines in recent years in India When the toxic substance and/or the hypothetical antagonistic substance have been identified it will probably be possible to take more specific measures but it has been shown that a high protein diet largely of animal origin will usually arrest though not reverse, the pathogenic processes There is little evidence that any improvement can be obtained by treatment when paresis has developed

PROGNOSIS

The vital functions are not involved and the expectation of life is not directly affected but the patients who are mostly of the uneducated agricultural class, become dependent on charity for their subsistence

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INFANTILE CIRRHOSIS OF THE LIVER*

Introduction —In private practice, more than in hospital practice in eastern India it is not uncommon to encounter children with a definite enlargement of the liver for which no obvious cause is found The enlarge ted with irregular fever eated early or if it osis of the liver soon

EPIDEMIOLOGY

Incidence —*Hospital reports in India do not usually reflect the true* state of affairs, as parents will not bring their children to hospital In a series of 1,100 children investigated by Rao (1934) in Vizagapatam en- hich 28 (or 2 5 per cent) the figure 1,748 for the 393 and recent Calcutta 300 deaths a year It is *more common in urban than in rural populations*

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Geographical distribution—The disease is particularly common on the eastern side of India, in Bengal Madras and Mysore, but cases are reported from Bihar, Orissa, and the Central and United Provinces' It is not seen in hill stations

Age, sex, race, and social status—Children between the ages of six months to two years (the dentition period) are most commonly affected, but the disease is sometimes seen in older children

Children of both sexes are affected but possibly there is a slight male predominance It is popularly said that the first male child after a series of females is likely to be affected, the explanation might be that it is the most pampered child who will be likely to have artificial and unsuitable food pressed upon it

The disease has a remarkable predilection for the Hindu community, and is most common amongst orthodox Hindus who are strict vegetarians In the series of 1,748 cases referred to above 1 616 were in Hindus, and Narayanamurthi and Tirumurthi (1939) reported a series of 445 cases in which none were either Mohammedans or Anglo Indians

The vast majority of the children come from middle class families

Heredity—There is a strong indication of an hereditary tendency it is usual for several children in the same family to suffer as each reaches the crucial age

ÆTIOLOGY

This is obscure Inherited predisposition and defective feeding are the most [illegible] c repeated child-births, and an [illegible] s and the child s health The [illegible] and artificial feeding is started [illegible] sweets fats (buffalo milk) are given the vitamins are not considered and the protein intake is low The child suffers from gastro intestinal upsets and the toxins that are absorbed are not properly dealt with by the liver Possibly an inborn error renders the liver cells peculiarly vulnerable to toxins and/or dietary (protein) deficiency, and they undergo premature degenerative changes

PATHOLOGY

As a result of the toxic action and/or disordered metabolism, there is fatty infiltration and later the liver cells become necrosed and are absorbed The healthy cells multiply to replace the loss and there is also a secondary fibrotic change commencing in the centre of the lobule The fibrous tissue develops within the lobule between the cells (intercellular cirrhosis) With the regeneration of the liver cells, there is also formation of new biliary channels In the advanced stage portal cirrhosis supervenes with the resultant ascites and jaundice

Blood Picture—There is a very distinct microcytic anæmia and a pronounced leucocytosis The latter is usually between 15 and 20 thousand per c mm but the normal proportions of the differential count are maintained

SYMPTOMATOLOGY

The onset is insidious During the prodromal stage the child, although appearing well-nourished, becomes peevish, irritable, and refuses food He

lower normal levels of hæmoglobin often existed Figure are given from a manganese mine where malaria was endemic and from tea estate labour forces where both hookworm infection and malaria were prevalent the subjects were ordinary workers selected at random after the grossly (clinically) anæmic individuals had been excluded The manganese mine recruits were mostly under nourished but showed no heavy parasitic infection

THE CAUSES OF ANÆMIA IN THE TROPICS

From the data given above it will be clear that climate *per se* does not cause anæmia What then are the causes of anæmia in the tropics? This anæmia varies in its degree and nature in much the same way as does the anæmia that occurs in temperate climates and it is susceptible to classification along the same lines

Classification of anæmia—The causes of anæmia will be appreciated

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tion of the average man there are about twenty five million million red cells and the duration of the life of a red cell is probably on the average about 75 days which means that in order to maintain the circulating red cells at a constant level about three hundred and thirty three thousand million new red cells have to be produced by the hæmopoietic tissues daily to replace the three hundred and thirty three thousand million obsolete ones *that disintegrate or are otherwise withdrawn and disposed of by the hæmolytic tissues* Production and destruction have to be balanced and any

to be made good The body is capable

there is failure of production if there

if there is excessive destruction anæmia

must eventually result therefore anæmia may be caused by (*a*) errors of erythrogenesis (*b*) loss of circulating blood or (*c*) errors of erythrolysis and it will be convenient to classify the causes of anæmia under these three major headings

The following table (Napier 193

of the anæmias in general with exam

the anæmia of each particular group

cosmopolitan diseases but wherever

cluded

Specific causes of anæmia in the tropics—These are (*a*) infections (*b*) dietary deficiencies or more commonly a combination of these two causes and (*c*) congenital defects It will be convenient to consider the subject under these three headings with the full appreciation of the fact that the division is an artificial one

In the appropriate places in this book reference has usually been made to the blood picture in the diseases in which anæmia is a prominent symptom but it will be worth reconsidering the subject here

ANÆMIA DUE TO INFECTIONS

Malaria—This is probably the most *important source of anæmia in* the tropics The most obvious cause of the anæmia is the destruction of the red cells by the parasite that is it is a hæmolytic type of anæmia due to the error of erythrolysis III A (*iv*) in the above classification but there

A Classification of the Anæmias

Main groups	Sub-groups	Examples of syndrome	General character of blood picture etc	Principles of treatment
I	A *Aplastic or hypoplastic of toxic or mechanical origin, due to —*			
	(i) unknown causes	Idiopathic aplastic anæmia	Usually normocytic normochromic reticulocytes—few van den Bergh—neg urobilin—absent	Remove cause Transfuse to tide over critical period and in extreme cases repeat periodically to supply blood needs
	(ii) (a) bacterial or other parasitic toxins	Anæmia of many acute and chronic infections including tropical diseases, e g *relapsing fever* and *Malta fever*		
	(b) metabolic toxins,	Anæmia of nephritis		
	(iii) chemical and physical poisons	Anæmia caused by benzol lead, sulphonamides radium and x rays		
	(iv) mechanical interference with blood formation	Carcinomatosis Albers Schonberg disease *anæmia of kala-azar*		
	(v) exhaustion of the bone-marrow	Terminal condition in many hyperplastic anæmias		
	B *Nutritional dysplasias* —			
	(i) Iron deficiency			
	(a) Actual	Hypochromic anæmia of infants invalids and others	Microcytic hypochromic reticulocytes few van den Bergh—neg normoblasts present urobilin—no increase	Supply excess of iron by mouth Ferrous sulphate gr xv daily for three weeks
ERRORS OF ERYTHROGENESIS	(b) Relative	Hypochromic anæmia of pregnancy and *hookworm infection*		
	(c) Failure of absorption	Simple achlorhydric anæmia		
	(ii) Deficiency of hæmopoietic principle		Macrocytic hyperchromic	Supply deficiency by giving liver extract
	(a) Absence of intrinsic factor	Addisonian pernicious anæmia	(a) reticulocytes + megaloblasts van den Bergh + achlorhydria	(a) Refined liver extract parenterally or liver by mouth
	(b) Absence of extrinsic factor		(b) van den Bergh—neg and reticulocytes—few	(b) Crude liver extract and marmite
	α) Actual	*Idiopathic tropical macrocytic anæmia*		
	β) Relative or conditioned	*Tropical macrocytic anæmia of pregnancy*		
	(c) Failure of absorption	*Anæmia of sprue*	(c) urobilin—no increase so or hypochlorhydria	(c) Liver extract parenterally
	(d) Failure of storage	Anæmia of liver disease		
	(e) Failure of utilization	Achrestic anæmia		
	(iii) Deficiency of vitamin C	Hypochromic anæmia of vitamin C deficiency		

A Classification of the Anæmias

Main groups	Sub-groups	Examples of syndrome	General character of blood picture, etc	Principles of treatment
II LOSS OF BLOOD FROM CIRCULATION TRUE SECONDARY ANÆMIA	Due to hæmorrhage, external, from mucous surfaces, or into serous cavities		The blood picture will depend *on whether the hæmorrhage* is acute or chronic *Acute* *normocytic* normochromic reticulocytes + + *Chronic* microcytic hypochromic reticulocytes + or ± van den Bergh—negative normoblasts present urobilin—no increase	Stop bleeding and remove cause where possible
	A Following external or internal injury	Severed artery, ruptured spleen, etc		*Transfusion*
	B Associated with disease of tissues	Hæmorrhoids, gastric ulcer, hæmoptysis, *dysentery*—amœbic, *bacillary* or metazoal, vesical *schistomiasis*		Supply iron in excess and give good protein and vitamin diet
	C Associated with hæmorrhagic states	*Scurvy, snake (viper) bite*		
	D Associated with blood sucking parasites	*Hookworm, hirudiasis*		
III ORS LYSIS	A Conditions affecting red cells and making them more susceptible to normal lytic processes (i) Abnormal red-cell structure, (ii) Abnormal physical condition of red cells, *e g* spherocytes, (iii) Effect of toxins, chemical poisons, etc , (iv) Parasitization	*Sickle-celled anæmia* Acholuric jaundice, paroxysmal hæmoglobinuria Lead poisoning arsenical drug poisoning *Malaria* and *oroya fever*	Normocytic or slightly macrocytic normochromic reticulocytes + + van den Bergh + + urobilin + + increased fragility of red cells	When known and when possible remove cause, *e g* malaria parasites by specific treatment Provide hæmopoietic substances in food, protein, vitamins and liver fraction
	B Conditions causing overaction of the erythrolytic tissues	Chronic *malarial* splenomegaly, possibly *kala-azar*	*ditto* decreased fragility of red cells	Remove cause in chronic splenomegaly remove spleen

is evidence that the anæmia is disproportionate to the blood parasite rate so that some additional explanation for the anæmia must be found. Certain observations suggest that there is a toxin which depresses blood formation as long as the malaria infection is uncontrolled so that it might also be classified as a toxic hypoplastic anæmia I A (ii) (c) in table XXIX

Further when there is very extensive red cell destruction especially if the patient has been repeatedly subjected to these attacks the blood forming material stored in the body becomes exhausted. Most of the iron is stored and re-utilized but some of the other hæmopoietic elements apparently need replenishing, in such cases a macrocytic anæmia sometimes develops which does not improve spontaneously as the anæmia of malaria usually does once the infection is under control but it responds immediately with a sharp reticulocytosis when liver extract is given. This would bring the anæmia into the group of relative or 'conditioned' nutritional dysplasias I B (ii) (b) (β)

It is frequently stated that the anæmia of chronic malaria is a hypochromic microcytic anæmia. While the writer believes that this is largely a misconception through the frequent association of chronic malaria with other anæmia producing conditions e g hookworm disease and dietary deficiency, there is one possible source of iron loss that should not be overlooked namely, the fixation of hæmatin in the form of insoluble hæmozoin pigment. It is therefore possible that in some persons on a low-iron intake this source of loss may upset the iron balance and introduce an iron-deficiency element into the anæmia I B (i) (b)

Finally, in certain persons subjected to malarial infection for many years through constant stimulation there is an overgrowth of the hæmolytic tissues in the body e g in the spleen leading to a constant excessive destruction of red cells, this places the anæmia in group III B

One might expect the anæmia of **blackwater fever** to show an iron deficiency element in view of the loss of hæmoglobin that occurs through the kidneys, apparently however the amount thus lost if it is insufficient to do irreparable damage to the kidney and kill the patient does not constitute a serious iron loss so that this element in the anæmia is overshadowed and a macrocytic anæmia that often necessitates the administration of liver extract (the 'conditioned' nutritional dysplasia mentioned above) is the more usual result of a blackwater fever attack

It is thus apparent that the anæmia of malaria is very complex and it is perhaps not surprising that writers have been reluctant to commit themselves to a clear cut statement as to what is the characteristic anæmia of this disease

In the malarial attack in the partially immune there is often little evidence of anæmia which suggests that some immunity to the malarial 'toxin' develops. If such a person is given specific treatment for the malaria immediately, the anæmia can usually be ignored. However, in the non immune adult and in children anæmia is fairly constant

Th[illegible] vary with the circumstances [illegible] attack that is not brought [illegible] reduced by as much as two [illegible] in a blackwater fever attack [illegible] far more gradual and seldom so extreme

In the well nourished person with an acute malarial attack return to normal is usually spontaneous once the red cell destruction and the toxin production ceases When in such a case the hæmoglobin fails to return to normal and there is a persistent reticulocytosis an early relapse *of malaria may usually be anticipated the recognition of this* residual anæmia is sometimes of diagnostic value when malaria parasites are scanty In the ill nourished and debilitated it may be necessary to supply some of the blood forming elements in the form of liver extract marmite and even iron to ensure an early return to normal If the patient has been subjected to repeated attacks over a long period the hæmolytic tissues are hypertrophied and disorganized and in order to adjust the dyscrasia and balance hæmopiesis whole liver principle (crude liver extract) may have to be given as in the previous case Finally in extreme cases it may be advisable to remove or put out of action a large portion of the reticulo endothelial system by removing the spleen or tying the splenic artery

Ancylostomiasis —This is probably the second most important source of anæmia in the tropics The cause is almost entirely blood loss from the bowel as a result *of the profligate blood sucking by the adult worm* this makes it a true chronic secondary anæmia II D which is usually markedly microcytic and hypochromic In heavy infections no amount of dietary iron is sufficient to compensate the iron loss but in moderate infections the loss of blood is such that it could be compensated if the individual were on a good iron intake but when the subject is taking a diet containing only the minimal iron requirements this extra loss is sufficient to upset the balance and produce an anæmia that can be classed as a conditioned iron deficiency anæmia I B (i) (*b*)

Even when an excess of iron is given however there are some instances in which the hæmoglobin level does not reach normal so that there is possibly a toxic element also in this anæmia which would place it in group I A (*ii*) (*a*) The degree of anæmia may be very extreme and there are few conditions other than ancylostomiasis and hæmorrhage that will produce a microcytic hypochromic *anæmia of this degree when the hæmoglobin* is as low as 2 grammes per 100 c cm in a patient obviously not *in extremis* this infection should always be suspected

Return to the normal hæmoglobin level follows adequate iron administration even without worm removal except in the few instances referred to above The worms must however be removed or the anæmia will return (see ANCYLOSTOMIASIS)

On the other hand the activity of the macrophages is stimulated so

Under specific treatment for kala azar the reticulocytes return to normal and there is a steady improvement in the blood picture but the

normal may not be reached for several weeks The administration of hæmatinics does not usually cause any material increase in the rate of improvement

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III A
(iv)

Trypanosomiasis—Anæmia is not usually marked in the early stages of the disease and any anæmia that occurs is probably of toxic origin In the later stages in the native patients it is often very striking and is certainly mainly nutritional in origin This class of patient becomes lethargic and indifferent to his dietary needs and lacks the energy to work to earn his food

Acute febrile conditions—The mechanism of the anæmia is not very clear in most of these conditions though a degree of anæmia is common One must conclude that the anæmia is mainly due to a toxic hypoplasia I A (ii) (a)

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group II C

In *yellow fever*, *Weil's disease* and *relapsing fever* again anæmia is not usually prominent The jaundice that occurs is not hæmolytic in origin but hepatic and it is due to the failure of the damaged liver cells in disposing of the products of the normal quota of destroyed red cells Such anæmia as occurs must also be toxic in origin

In *brucellosis* the anæmia may be considerable in proportion to the severity of the disease This suggests that there is a specific action by the bacterial toxins on the hæmopoietic tissues and the anæmia must be grouped as I A (ii) (a)

Dysentery—*Any severe dysentery whether it is caused by bacteria* protozoa or metazoa may produce an anæmia of the true secondary type that is due to loss of blood II B This of course may be acute but it is more frequently subacute or chronic

In the later stages of these infections the anæmia is due mainly to malabsorption *it is a nutritional dysplasia I B either sub group (i) (c)* or (ii) (c), usually both elements being apparent

In chronic amœbiasis it has been suggested that the anæmia is due to toxic absorption from the intestinal tract but the evidence for this is not entirely satisfactory, this would place it in group I A (ii)

The anæmia of amœbic hepatitis and liver abscess is often very marked it is usually normocytic or macrocytic It can be classified as I B (ii) (d) As the bowel condition improves the blood picture returns slowly to normal but the rate of improvement is accelerated considerably by the administration of liver extract and in some cases this must be considered an essential *part of the treatment*

Other helminthic infections—*Diphyllobothrium latum* has been reputed to cause a pern

ship of this worm to the anæmia is still in question However, a fatty-acid that is capable of causing a macrocytic anæmia in experimental animals has been isolated from this worm, it is therefore possible that this anæmia is a hypoplastic dysplasia of toxic origin, I A (ii) (a)

The schistosomes produce an anæmia of the secondary type by causing *blood loss in the bowel and bladder but there is evidence that they also are capable of causing some anæmia by their 'toxins' in the earlier stages of* the infection, and in the later stages by the damage to the bowel, which will cause failure of absorption of essential hæmopoietic substances, and to the liver which will cause failure of their storage

ANÆMIA DUE TO DIETARY DEFICIENCIES

Tropical Macrocytic Anæmia

History —*In 1929* under the title malignant anæmia of the tropics" Mackie drew attention to an anæmia which he had observed twenty years earlier that

Two years later Wills
arly common amongst
omen was curable by
called the condition
rimarily a nutritional

ing the same condition Mackie who
ad made many years before did not
a except regarding the degree of the
the cases the colour index was above
s a macrocytic non hæmolytic anæmia

ÆTIOLOGY

It is possible that in a few instances tropical macrocytic anæmia (TMA) is a pure dietary deficiency, but there is strong evidence that, in the majority of cases, it is a 'conditioned deficiency' in which bowel

art *The deficient dietary*
iated with the vitamin B.
fraction

In tropical macrocytic anæmia hæmolytica there is always a history of repeated attacks of malaria in childhood and adolescence, and there is usually a large spleen Apparently there is overaction of the hæmolytic tissues which destroy red cells in excess, these have to be replaced, so that there is a greater demand for hæmopoietic substances than can be met by the low dietary intake of the patient and 'relative' nutritional anæmia develops The iron is recovered and re-utilized so that the anæmia is of the macrocytic type

Tropical macrocytic anæmia of pregnancy occurs amongst women of the poor-dietary classes usually with a previous history of dysentery and/or

malaria they are mostly vegetarians whose protein intake is low and though a particularly low vitamin B complex intake has not always been demonstrated a marked improvement sometimes follows the administration of this vitamin in the form of marmite However the absence of any appreciable response in the presence of the fœtus and the rapid recovery in all moderately severe cases after its removal at term or prematurely suggest the possible action of a pregnancy toxin producing a conditioned deficiency

Another suggestion is that it is a relative deficiency like that known to occur in the case of iron deficiency in pregnant women but the positions are not parallel because the infantile mortality is very high in TMA suggesting that the fœtus also suffers from a deficiency whereas in iron deficiency anæmia the infant takes all the iron it requires and the infantile mortality is low

Thus to summarize tropical macrocytic anæmia may be (i) a pure dietary deficiency (ii) it may be due to a combination of a poor diet and poor absorption when it is associated with definite bowel syndromes such as sprue or para sprue (iii) it may be due to a combination of a poor diet and repeated malarial infections or (iv) it may be due to the super addition of pregnancy to any of these three causes or to any combination of them

EPIDEMIOLOGY

Since this condition was first described several instances of the pregnancy form have been reported from temperate countries but it is nevertheless essentially a disease of backward tropical countries It has been shown to be prevalent in India Malaya tropical Africa the West Indies and South America and will probably be found to occur in every tropical country where it is sought

It occurs mainly in the poor economic classes of the natives or settlers in tropical countries It may occur at almost any age but it is more common in late adolescence and early adult life and partly because of the association with pregnancy it is more common amongst women than men but it occurs in both sexes It was more frequently observed in first and second pregnancies

T in the ith the (April to October)

PATHOLOGY

Our knowledge of the morbid anatomy of the condition is very poor and in the few post mortem examinations that have been performed the associated diseases clouded the picture

Blood picture—The anæmia may be extreme and figures as low as 500 000 red cells per c mm and 2 grammes of hæmoglobin per 100 c cm of blood are sometimes recorded though in the majority of cases the red cell count will not be much below 2 000 000 per c mm The red cells are macrocytic usually between 100 and 150 c μ the mean corpuscular hæmoglobin between 30 and 40 $\gamma\gamma$ and the mean corpuscular hæmoglobin concentration between 33 and 37 per cent so that the anæmia is ordinarily a normochromic one The Price-Jones curve is shifted to the right but tends to retain its normal shape and is not usually a low spread out curve

terally, and in fact in some cases this seems to tip the balance and cause a complete remission of all symptoms, although in the fully-developed syndrome dietetic treatment also is necessary

ANÆMIA DUE TO CONGENITAL DEFECTS

Sickle-celled anæmia which is confined to negroes, though most of the studies of
negroes in
anæmia o
sidered tropical, this disease again has been studied mainly in the United States, but nearly all the subjects have been of Mediterranean stock, Italian, Greek, Armenian, or Syrian However, several cases have been

climate

A short description of the former two conditions will be given here

Sickle-celled anæmia —This disease must not be confused with the sickle-cell trait ('sicklæmia'), a condition relatively common amongst *individuals of negro stock, occurring in 7 3 per cent of 8 453 negroes (Diggs et al* 1933), but not necessarily associated with any morbidity, this trait is transmitted hereditarily as a dominant Mendelian characteristic

Sickle-celled anæmia occurs in about 1 in 40 negroes with the sickle-cell trait Few authentic cases have been reported in persons without some admixture of negro blood The condition has been diagnosed during the first year of life, most patients come under observation during the first two decades and they seldom survive the third decade

Pathogenesis —The sickling phenomenon is associated with 'reduction *of the hæmoglobin in the cell, in vitro, and apparently also in vivo* as for example when a local anoxæmia is caused by constriction of a finger The shape of the red cell can be restored by oxygenation of the blood When this sickling occurs in the capillaries of the tissues, an aggregation of the sickled cells apparently results, and stasis and occlusion may follow Many *of the symptoms, for example,* the painful crises in the spleen and elsewhere, the heart changes, the secondary pulmonary changes and the ulceration in the legs may be caused by vascular occlusion in different organs and tissues The compensatory hyperplasia of the bone-marrow will account for the bony changes

The hæmolytic blood picture and the anæmia are caused by the early hæmolysis of the defective sickle cells which in turn leads to the vicious cycle of anoxæmia and further sickling This anæmia may be classified as III A (i)

Blood picture —The red cells are reduced to 2 000 000 or even 1,000-000 per c mm and the h The mean
corpuscular hæmoglobin
the cell will depend enti
in vivo and *in vitro*, for
of local venous congestic
show normal or small si
reticulocyte percentage is between 5 and 25 per cent Normoblasts are constantly present, from 1 to 10 per 100 leucocytes In a rapidly drawn

sample taken without much previous venous congestion there are usually a few sickle cells present, but if a sealed wet preparation is made the majority of the cells will develop into the sickle or some other bizarre shape within a few hours The erythrocyte sedimentation rate (ESR) will vary with the degree of oxygenation A sample taken after a period of local venous congestion will show a very slow ESR, from 1 to 4 mm in one hour, *whatever the degree of anæmia,* but this same sample will usually show a rapid ESR, up to 70 mm or more in one hour, according to the degree of anæmia, after oxygenation

There is a leucocytosis with a large mononuclear increase and a left-ward shift in the Arneth count

The indirect van den Bergh reaction is strongly positive

Symptomatology.—The patient may suffer from a considerable degree of anæmia before any special symptoms develop, and there is usually a history of periodic attacks with symptom free intermissions

The main symptoms beyond those directly attributable to the anæmia namely weakness and breathlessness on exertion, are fever—which may be a low irregular fever or rise to 103° or so, pains in the joints, pains in the abdomen—that may simulate an acute abdominal emergency enlarged and painful spleen, cardiac dilation, various neurological manifestations chronic leg ulceration—similar to varicose ulcers and bony deformities—sabre tibia scoliosis and kyphosis

Roentgenological examination of the bones shows osteoporosis or osteosclerosis, and hair-on-end thickening of the skull In the retina there is a very marked tortuosity of the vessels

Diagnosis—Sickling alone is not evidence of sickle-celled anæmia, but in sickle celled anæmia, if the blood is taken from a vein with an air free syringe (dead space filled with liquid paraffin) and injected into 10 per cent neutral formaldehyde in 0 85 per cent saline 30 to 60 per cent of the cells will be sickled, whereas only an occasional sickled cell will be found in the patient who simply has the sickle-cell tendency

The following simple method of diagnosis is recommended by Winsor and Burch (1944)

A sphygmomanometer cuff is placed on the arm and inflated sufficiently to stop the venous return for 6 minutes A sample of 5 c cm of blood is taken into an air free syringe and transferred to a small tube or bottle of the same capacity containing 3 mg of dry ammonium oxalate and 2 mg of dry potassium oxalate this is immediately corked and rotated gently between the palms to ensure oxalation of the sample Part of the sample is filled immediately into a Wintrobe's tube which is corked and placed in a vertical position in a suitable rack The rest of the sample is transferred to a Erlenmeyer flask rotated for 15 minutes until the sample is thoroughly oxygenated (this will be apparent from the bright red colour of the blood) and filled into another Wintrobe's tube In most cases of sickle-celled anæmia the difference between the sedimentation rates in the two tubes after an hour will be 60 or 70 mm but a difference of 20 mm which may be observed after as short a time as 15 minutes indicates sickle-celled anæmia or at least the sickle-cell trait

Treatment—This is symptomatic only

Prognosis—This is always bad, temporary improvements will often occur, but death usually occurs within the first three decades

Cooley's anæmia—This syndrome has recently been separated from the more comprehensive von Jaksch's syndrome As indicated above it was

first believed to be confined to individuals of Mediterranean stock, but has recently been reported in several Indian children (Napier, Shorten, and Das Gupta 1939) and one Chinese (Foster, 1940).

The most characteristic feature of the disease is the bony changes In the long bones there is an increase in the medulla with thinning of the compact bone The general decrease in the density of the medulla leaves the trabeculæ standing out, forming a characteristic mosaic pattern in the *x*-ray picture In the skull the diploe is thickened to several times its natural thickness with perpendicular striations standing out to give the appearance of hair standing erect on the inner plate of the skull, the outer-plate being invisible

The blood picture is less characteristic and has features common to other examples of the von Jaksch's syndrome The degree of anæmia is variable but often considerable The erythrocytes vary considerably in size from extreme microcytosis to extreme macrocytosis, but the mean corpuscular hæmoglobin is low, so that the anæmia is hypochromic There are frequently 'target' cells present, and many of the red cells are distorted and fragmented There are many nucleated red cells, mostly normoblasts and always a distinct and sometimes a marked—up to 50,000 per c mm — leucocytosis The van den Bergh reaction indirect, is usually positive

The anæmia and the large head are the most striking clinical features

The steady progress towards a fatal termination is usually uninterrupted If the symptoms appear in the first year of life death usually occurs within six months, if however they do not appear until later, the child may survive several years Death is usually due to intercurrent infection

INVESTIGATING ANÆMIA

The causes of anæmia in the tropics are thus numerous and varied *Whenever anæmia is suspected in an individual, or in a group of indi*

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sedimentation rate estimations, the van den Bergh tests gastric analysis and sternal puncture, should be carried out In the case of a group these examinations should be done on a random sample of the group with if

al population The possible causes

X), the necessary *parasitological*

he diets should be reviewed and

ade

With these data and the aid of table XXIX, it should be possible to arrive at a satisfactory conclusion as to the cause of the anæmia Although the cause even in one individual, is seldom a single factor, the correction of one factor will often reduce the anæmia to negligible proportions

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SNAKES AND SNAKE-BITE*

SNAKE-BITE

* By Major S K Ganguli I M S lately assistant professor of entomology Calcutta School of Tropical Medicine and the author

Introduction—The practical importance to the ordinary practitioner of any knowledge regarding snakes and snake bite is often questioned by

he will cer
quite unable
brought to

Further it is the duty of a practitioner in a tropical country to familiarize himself with the commoner snakes in the locality and this he cannot hope to do without a knowledge of the essentials of herpetology This study is important from two points of view—firstly in order to be able to recognize ... poisonous snakes and secondly to
they may not be destroyed un
are often useful members of the
frighten away rodents and also
smaller poisonous snakes

CLASSIFICATION

Snakes belong to the class REPTILIA

The class REPTILIA is divided into twelve orders of which eight are extinct Extant reptiles belong to four orders

1 Crocodilia—crocodiles, alligators and gavials
2 Chelonia—tortoises turtles and terrapins
3 Rhynchocephalia—represented by a single living species the Tuatera or Sphenodon (*Hatteria punctata*) of New Zealand a lizard like reptile in which the traces of the median eye can still be made out
4 Squamata—snakes, lizards, and chamæleons

The order Squamata is divided into three sub-orders of which two are still extant, namely

(i) Ophidia (or Serpentes)—snakes

(ii) *Lacertilia*—lizards and chamæleons

In the sub order Ophidia (snakes), about twenty-four hundred species have been described, of which over three hundred are sufficiently poisonous to cause fatal effects in man In India including Burma and Ceylon there are at least 330 species of snakes of which about 70 are poisonous to man (40 terrestrial and 30 marine species), this is the only country in which all the families and sub families are represented

There are nine families (1) Typhlopidæ, (2) Leptotyphlopidæ, (3) Anilidæ, (4) Boidæ, (5) Uropeltidæ, (6) Xenopeltidæ, (7) Amblycephalidæ, (8) Colubridæ, (9) Viperidæ

The family *Boidæ* includes several of the largest constrictor snakes In it there are two sub-families, Pythoninæ and Boinæ, the former includes *Python repticulatus*, the regal python, the largest snake in the world, which attains a proven length of thirty-three feet, and the latter, *Constrictor constrictor* the boa-constrictor The Boidæ are not poisonous but kill their larger prey by coiling around them and crushing them

All the species of the first seven families are non-poisonous, the last two families include all the poisonous snakes The *Colubridæ* are divided ... poisonous, three are mildly ... the *Viperidæ* there are two ... ous

The sub-families of the *Colubridæ* and *Viperidæ* are sometimes grouped according to the nature and position of their fangs, if these are absent, as in the three non-poisonous sub-families of the *Colubridæ*, the snakes are known as 'Aglypha' (γλυφη=a groove), if the fangs are behind the teeth they are known as 'opisthoglypha' (οπισθου=behind), if the fangs are developed from the front teeth and are grooved, they are known as 'proteroglypha' (προτερου=before), and if the fangs are hollow tubes (like hypodermic-syringe needles) they are known as 'solenoglypha' (σωληυ= tube) ... mous mildly poisonou ... f *Colubridæ*, and the ... the position of their ... m into man, but their ... prey by this means

The families and sub-families of the sub order Ophidia, with their main characteristics and commoner species, are shown in Table XXX (*a*) and (*b*)

IDENTIFICATION

The identification of the species of a snake is a highly technical procedure that is the domain of the zoologist, or more especially the herpetologist, it takes account of the characteristics of bones and teeth and of ... of the scales as well as the general shape and size of the ... external characteristics alone ... e a provisional identification ... Table XXXI

Poisonous or non-poisonous?—For practical purposes, it will usually be sufficient to distinguish between the poisonous and the non-poisonous species of snakes

TABLE XXX (a)

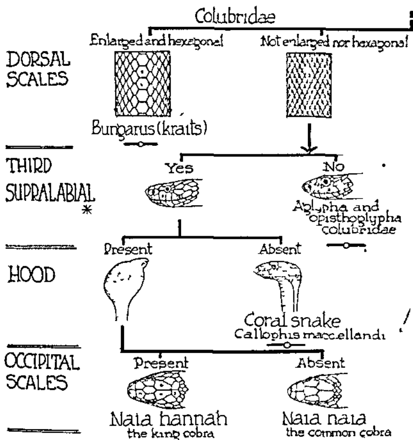
Classification of Snakes

Family	*Examples*	*Habitat*
1 *Typhlopidæ* (non-poisonous) Small worm-like burrowing snakes uniform small scales maxilla toothed mandible bare Tail small usually as thick as the head end Distribution—widespread in tropics Species—over 100	*Typhlops braminus* *T diardi* *T proximus*	Tropical Asia including India Tropical Africa India Australia
2 *Leptotyphlopidæ* or *Glauconiidæ* (non-poisonous) Resembles the preceding family except maxilla bare mandible toothed tail long Distribution—cosmopolitan Species—over 30	*Glauconia blanfordi* *Leptotyphlops dulcis*	India North America
3 *Aniliidæ* or *Ilysiidæ* (non poisonous) Burrowing snakes of variegated colour usually about 2½ to 3 feet long claw like spur at the vent representing vestigial remnants of hind limbs ventral shields slightly enlarged Species—6	*Cylindrophis rufus* *C maculatus* *Ilysia scytale*	South-east Asia Ceylon Tropical America
4 *Boidæ* (non-poisonous) Includes several largest constricting serpents claw like spurs at vent which are much longer than in the preceding family very large number of scales on the dorsum of the body Ventrals are moderately enlarged but do not stretch across abdomen		
Sub-family —		
(i) *Pythoninæ* Supra-orbital bone present Premaxilla—toothed Species—over 20	*Python molurus* (The rock python) *P reticulatus* (The regal python) *P spilotes* *Liasis fuscus*	South-east Asia India Burma Malaya peninsula etc Australia New Guinea, N Australia
(ii) *Boinæ* Supra-orbital bone present Premaxilla bare Species—about 40	*Constrictor constrictor* (Boa constrictor) *Eunectes murinus* (Anaconda) *Eryx conicus* (so-called two-headed snake) *E johnii* (so-called two-headed snake)	Tropical America Tropical S America India India

TABLE XXX (b)—(Contd.)

Family	Sub-family	Examples	Habitat
8. *Colubridæ*—(Contd.) Opisthoglypha Small fangs at the back of the maxilla Small poison glands	(iv) *Homalopsinæ* (mildly poisonous) *Ventrals slightly enlarged, do* not stretch across abdomen River and estuarine snakes Tail slightly compressed in many species Species—about 25	*Cerberus rhyncops*	India, S E Asia
		Hypsirhina enhydris	*India, S E India*
		H macleayi	Australia
	(v) *Elachistodontinæ* (mildly poisonous) Like Dasypeltinæ it possesses tooth like projections into the œsophagus to break birds' eggs Species—one	*Elachistodon westermanni*	North Bengal
	(vi) *Dipsadomorphinæ* (mildly poisonous) A parallel to sub-family Colubrinæ, comprising racers, arboreals, and semi aquatics of various size and shape Species—about 300	*Dryophis mycterizans*—The green whip snake	S E Asia, India
		Chrysopelea ornata	
		Dipsadomorphus trigonatus—The cat snake	
		D dendrophilus	Malaya peninsula
		Dispholidus typus—The boomslang	South Africa
		Pseudoboa clœlia—Mussurana	Tropical America
Proteroglypha Anterior maxillary teeth grooved (fangs), which are erect and small, connected with highly developed venom glands, venom—neurotoxic	(vii) *Elapinæ* (highly poisonous) Terrestrial, arboreal or semi-aquatic in habits Tail cylindrical and tapering Ventrals very much enlarged and stretch across abdomen They are among the most deadly of all serpents Species—about 180	*Naia naia*—The common cobra	Tropical Asia including India
		N hannah—The king cobra	South-eastern Asia
		N haje—The Egyptian cobra or asp.	North Africa
		N nigricollis—The spitting cobra	Africa
		N flava—The cape cobra	South Africa
		Bungarus candidus—The common krait	India
		B fasciatus—The banded krait	India and South-eastern Asia
		Dendraspis angusticeps—Mamba	Africa
		Pseudechis porphyriacus—The black snake	Australia
		Notechis scutatus—The tiger snake	"
		Acanthophis antarcticus—The death adder	"
		Denisonia superba—Australian copper head	"
		Callophis macclellandi—Coral snake	Eastern India, Southern China, Burma
		Micrurus fulvius—The harlequin snake	North America

Family	Sub-family	Examples	Habitat
8 *Colubridæ*—(Contd) Proteroglypha	(viii) *Hydrophinæ* (highly poisonous) Sea snakes. *Tail flat oar-shaped* Ventrals either slightly or not enlarged Nostrils open at the upper surface of snout Species—over 50	*Enhydrina valakadien* *Distira robusta* *Hydrus platurus*	Indian Ocean, Tropical Pacific Ocean of Asia and Australia.
		Pelamydrus platurus	Pacific ocean along Tropical America.
9 *Viperidæ* (highly poisonous) Usually triangular head distinct and differentiated from a thick body by a narrower neck tail short Pupils vertically elliptical in most cases Ventral scales very much enlarged, stretching across abdomen Solenoglypha Anterior maxillary teeth are canaliculated (fangs) very large not always erect, can be folded under the palate connected with large venom gland The venom is hæmotoxic	(i) *Viperinæ* (highly poisonous) True or pitless vipers No loreal pit head scales small except in the genus *Azemiops* Distribution—Asia, Africa and Europe. Not found in America or Australia. Species—about 50	*Daboia*—The Russell s viper	India, Ceylon, Burma, Thailand
		Echis carinatus— Phoorsa'.	N Africa, S.W Asia. India
		Bitis arietans—The Puff Adder	S W Asia Africa
		B gabonica—The gaboon viper	Africa
		B nasicornis—The rhinoceros viper	Africa
		Vipera berus—The adder	Europe
		V aspis—The asp	Europe
		Azemiops feæ—The Fea s viper	Burma, China
	(ii) *Crotalinæ* (highly poisonous) Rattlesnakes. A *loreal pit* present between the eye and the nose and rattles on the tail Head scales small in Crotalus head shields in Sistrurus Distribution—America Not found in Europe Asia, Africa and Australia Species—about 30	*Crotalus confluentus*—The rattle snake	North America
		C adamanteus—Eastern diamond backed rattle snake	,,
		C atrox—Western diamond rattlesnake	,, ,,
		C horridus—The banded rattlesnake	
		C terrificus—The dog faced rattlesnake	,,
		Sistrurus catenatus—The Massasauga rattlesnake	
		S miliarius—The pigmy rattlesnake.	
	(iii) *Lachesinæ* (highly poisonous) A loreal pit but no rattles Small head scales except the genus *Agkistrodon* Distribution—America and Asia Species—about 70	*Agkistrodon mokasen*—The copper head	,,
		A piscivorus—The water moccasin or cotton mouth	,,
		A bilineatus—The tropical moccasin	Central America
		A himalyanus—The Himalayan pit viper	Himalayas
		A hypanale—The Karawala	Ceylon, South India
		Bothrops atrox—(*B lanceolatus*)—The Fer-de-lance	South & Central America, W Indies
		B jararaca—The Jararaca	South America
		B jararacussu—The Jararacussu	,, ,,
		Lachesis muta—The bushmaster	South & Central America
		Trimeresurus gramineus—The green pit viper	India, S E Asia East Indies
		T monticola—The large-spotted viper	Eastern India, Burma Southern China



Key Where the name is printed in large type it indicates that the species is a poisonous one, or if it is the name of a family subfamily or genus that all or many of its members are poisonous

For example, all HYDROPHINÆ or sea snakes are poisonous so are Crotalinæ, Lachesinæ and Viperinæ Colubridæ contain both poisonous and non-poisonous species

On the other hand the Typhlopidæ, etc are non-poisonous, so are the Amblycephalidæ Of the Colubridæ, Bungarus, *Naia hannah* and *Naia naia* are very poisonous. Coral snakes are poisonous but not so highly poisonous and the aglypha and opisthoglyphs Colubridæ are non-poisonous

(If this diagram is copied for class purposes the poisonous snakes should be printed in red ink)

* The third supralabial scale touches both the eye and the nasal scale in the poisonous Colubridæ

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Aglyphous	two rows of teeth on either side of the maxilla and no fangs	non-poisonous
Opisthoglyphous	two rows of teeth with one pair of grooved fangs at posterior end of outer row	mildly poisonous
Proteroglyphous		poisonous
Solenoglyphous	one row of teeth with a pair of long tubular movable fangs and one or more pairs of accessory fangs	poisonous

TABLE XXXI

Data required for identifying the species of a snake from its external characters

1) SIZE	(a) Length including the tail, (b) Length of the tail only
2) SHAPE OR FORM	(a) Tail—whether flat or cylindrical, tapering slender or *stumpy, bevelled* rounded or pointed, rattles present or not (b) *Body*—whether stout, moderate sized or slender (c) Head—whether distinct from the neck or not, broad or narrow, high or flat (i) Snout—pointed or obtuse (ii) snout (iii) (iv) lly or (v) (vi) Loreal pit between eyes and nostrils—present or not
3) COLORATION	Ground colour of the dorsum and ventrum, any colour pattern such as longitudinal and transverse markings stripes or streaks spot, rings or other markings Markings on the head and tail
4) ARRANGEMENT OF SCALES OR LEPIDOSIS	(a) Body and tail (i) Ventrals—whether broad moderate sized or narrow, then number entire in the mid their direction or or keeled hexagonal or *rhombic* (b) Head (i) Whether shields or scales if shields—then pattern shape and size (ii) Supra labials—their number and pattern especially the relation of the 3rd supra labial in the family *Colubridæ* (iii) Infra labials—their number and pattern (iv) Sub linguals—size and shape, whether the mental groove is present
5) ARRANGEMENT AND CHARACTER OF TEETH	(i) Whether both maxillæ and mandibles are toothed (ii) How many rows of teeth on the upper jaw (iii) Premaxilla toothed or not (iv) Fangs present or not, if present—whether anterior or posterior grooved or hollow tubes

* Great care should be exercised in examining recently killed snakes as muscular spasm may occur and many people have been bitten by a dead snake

COMMON POISONOUS SNAKES OF INDIA

1 Common cobra *Na a naia* A snake tl well mark d hool tle ma k n n tle b k of tle hood d ffer n d ffer nt colou an t l ft—b nocella e m ddle—ano ellate r gl t—monocellate Colour of tle body black b own l uff or wl eat-coloured rarely wh t sl Abdomen—wh te or yellow l Leng h—t to 6 feet or mo e g rtl—moderate *Lep do s* ven ral stretch ng acro abdomen l lls on the head th d supra lab al tou hes tle eye and tle nasal scale S b audals—d d d

2 K ng cobra *Na a hannah* Hood—not so well marked Length—usu lly 8 to a a ks n l l cro s lead w l es and t nasal s ale subcaudals—ent re ante orly d ded jo te orly

3. Common kra t *Bungarus cand dus* Length— all 3 o 4 feet Steel l la k n colo r l wl te l near arcl es across ba k *L p do s* entr ls s ret h ng a o abdom n sl elds on head vertebrals enlarged and l ex gonal subca d l — entire

4 B nded kra t *Bungarus fa c atus* A b g sto t n ke grow to abo t a to 6 f et or e en 7 feet long Bod w h l r e e low l blue l n o l an l Ta l—rather blunt Very slugg h n hab t *L p do s*—san 3

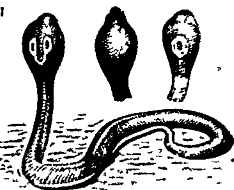
5 R ells per *Dabo a ru sell* Length—3 to 4 f t S ou body tr ng l r an l fl t lead la g yes w tl vert call ell pt l j l nu l j o nt short o a r ng l n Abdom n—wl e n ral t l l d

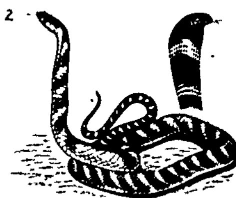
6 Saw-sc led per or Phoorsa *Ech ca natu* Sm ll n k u ll bo t 1½ fe t He d—tr angular w th d t nct wh e n k o er se bl g w nt of a l d Bo l colour—bro n b ff or s ndy w l a ga d culo j tern ary ng f om nd dual to ind dual Abdomen—w l w l m l ple sn all l k spo s *Lep dos s* ventrals stretcl ng acro s abdomen sm ll s al s on lea l s l caud ls ent re

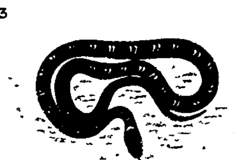
7 C m feet H d—fl t o —gree r el n r ls st et l

8 A sea sn ke *E l ydrina alakad en* A rob t n ke ta l fl t o sl ape l l ke all o her H lroph n No tr l—s t te l on tle l of o Colo r— v ry l le *Lep lo* en r l lgl tl enl r d l el l on tle l ea l

Plate D

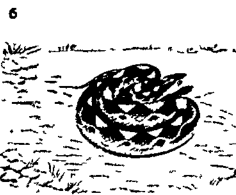


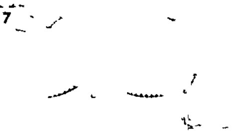


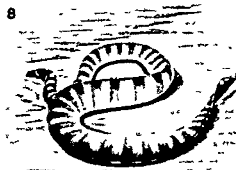












Snakes can also be identified with a fair degree of certainty
ing certain external characteristics, and using the scheme 'Ide
of Poisonous Snakes'

It is important to remember that colour is seldom of use a
tinguishing characteristic, the colour of most species is variable to a
or lesser degree However, plate D, will give some idea of the usu
of some of the more common Indian poisonous snakes

SNAKE-BITE

Epidemiology.—The geographical distribution of snake bite is
urally dependent on the geographical distribution of the dangerous sp
of venomous snakes, this can be seen from Table XXVI India the
Indies, tropical Africa and tropical America are the fields richest in sna
and India with at least 70 species of poisonous snakes heads the list

On the other hand, there are many islands that are free from terrestr
poisonous snakes, *e g* Iceland Ireland, New Zealand Madagascar Hawa
and many islands in the South Pacific and several in the West Indies

In Europe there are few poisonous snakes the most common are the
adder (*Vipera berus*) and the asp (*V aspis*)

In Australia, the commonest causes of snake bite death are the death
adder (*Acanthophis antarcticus*) the tiger snake (*Notechis scutatus*) and
the black snake (*Pseudechis porphyriacus*)

In Africa, the commonest deadly snakes are the mamba (*Dendraspis
angusticeps*), the spitting cobra (*Naja nigricollis*) the puff adder (*Bitis
arietans*), the rhinoceros viper (*B nasicornis*) the asp (*Naja haje*) and the
Cape cobra (*Naja flava*)

In North America poisonous snakes are relatively common in the moun-
tainous and marshy districts The best known are the rattlesnakes the
diamond backed rattlers (*Crotalus atrox* and *adamanteus*) the banded
rattlesnake (*C horridus*) and the massasauga (*Sistrurus catenatus*) the
rattleless pit vipers, the water moccasin or cotton-mouth (*Agkistrodon
piscivorus*) and the copperhead (*A mokasen*) and the harlequin (coral)
snake (*Micrurus fulvius*)

In South and Central America, the most feared snakes are the bush-
aster (*Lachesis muta*), the fer-de-lance (*Bothrops atrox*) and the jararaca
B jararaca), but there are many other species

In India, the cobras, the kraits, the Russell's viper and the echis viper
the snakes mainly responsible for the high mortality

In countries where poisonous snakes are abundant death from snake-
constitutes not an unimportant cause of mortality Between 20,000
5,000 deaths from snake-bite are reported annually in British India
gh snake-bite is sometimes a convenient euphemism for death by
e in other instances death from snake-bite will escape registration
, so that on the whole the figure probably represents something near
h On the other hand, in Australia between 1910 and 1926 the
annual deaths from snake-bite numbered less than 15 For the
he world the annual deaths from snake-bite are usually placed
n 5,000 and 10,000

Few snakes are aggressive as far as man and other large mammals ar concerned, and the majority bite only when attacked, frightened, or acci dentally injured The persons most affected therefore are the bare-foo villagers walking along a jungle path at night who may accidentally trea

house to escape unfavour
rain—and it is not uncom
e frequently she, places
hand into a receptacle in a dark corner

in and outside their huts, and th
bites
itage of cases in children, as th
toxic
between the amount of venom in
jected and the body weight of the subject

ANATOMY AND TOXICOLOGY

Poison apparatus.—This consists of a pair of poison glands connectec by ducts to the grooved or cannaliculated fangs on the maxillæ The poisor glands are modified supra-labial glands, analogous to the parotid gland of the mammals They occupy an intermuscular space in the temporal regions below and behind the orbit, on either side of the upper jaw (maxillæ)

The glands are enveloped by a fibrous capsule to which are partly attached the fibres of the masseter muscles and are surrounded by a group of muscles, consisting of the anterior, middle and posterior temporal, and the digastric During the act of striking, these muscles are involuntarily contracted and the glands are violently squeezed, so that the venom is driven along the duct to the grooved or cannaliculated fangs and thence to the tissues of the victim, even if the snake misses its victim, venom will sometimes be ejected The venom of the spitting cobra, *Naia nigricollis*, can be ejected a distance of 6 to 8 feet and it will cause temporary blindness if it comes in contact with the eyes In other species, especially the opisthoglyphæ, the actual pressure of the bite appears to be necessary to eject the venom

In the proteroglypha and solenoglypha, the fangs, which are situated anteriorly on the maxillæ, differ one from the other in their structure, size and shape In the proteroglypha (*Colubridæ*), the fangs, though slightly movable, are erect and small, the groove, which runs anteriorly lengthwise from t
covered by

when these muscles are relaxed, the fangs
ite inside a sheath of mucous membrane
(vagina dentis), but when the muscles are contracted for the strike or bite the fangs come forward automatically and project at a right angle from the

when the main fangs are broken

The venom.—Physical nature.—It is a colourless or golden-yellow

It is thermolabile and destroyed by the gastric juice

Quantity —The venom is collected either by compressing the gland or by the spontaneous bite of the snake on a parchment or rubber membrane spread over any convenient receptacle * The latter method gives a better yield The quantity of venom varies with each species and with the size of the individual from about 8 mg in the krait to 375 mg in the cobra

Chemical composition —The results of a broad analysis of the venoms of various snakes show that they consist of —

(1) Protein matter—albumin and globulin (coagulable by heat)—which forms the major portion
(2) substances of the nature of proteoses and peptones (not coagulable by heat)
(3) enzymes or ferments
(4) inorganic salts (chlorides phosphates, etc)
(5) a trace of fatty matter and
(6) colouring matter

Toxic principles —It was at one time generally believed that the coagulable proteins the non coagulable protein like substances and the enzymes were responsible for the toxicity of the venoms but separate toxic

)

snake *Crotalus adamanteus* crotalotoxin ($C_{34}H_{54}O_{21}$) It is believed that these substances are of the nature of glucosides free from nitrogen and belonging to the saponin group

The toxicological action of the venoms of different species of venomous snakes varies widely and depends upon the summation of various toxic principles present in the venom the proportions vary with each species The toxic principles are —

(1) neurotoxins with special affinity (a) for the nerve cells and particularly for the respiratory centre and/or (b) for the nerve terminations of the muscles especially for those of the diaphragm
(2)

etc
(3) an antifibrin ferment (protease) destroying the fibrinogen thus acting as an anti-coagulin
(4) a fibrin ferment (thrombase) causing thrombosis
(5) a proteolytic ferment and
(6) a cardiac toxin which in small quantities tones up the heart but in higher concentration stops it in systole

Selective action of different venoms —As a general rule the venoms of *Colubridæ* contain a predominating quantity of neurotoxins this is especially true of the common cobra the kraits the tiger snake, the black snake the death adder and the sea snakes In the cobra venom neurotoxins are responsible for 50 per cent of its toxicity hæmolysins and anticoagulins for about 40 per cent and a proteolytic ferment for the rest

On the other hand in the *Viperidæ* the venom as a rule contains a high proportion of hæmorrhagin Thus in the Russell's viper venom

* In India the snake charmers collect venom in the shell of a water mussel over which a palm leaf is tightly held The snake bites on the palm leaf and the poison trickles down into the cavity of the shell

hæmorrhagin represents about 70 to 75 per cent of the total toxicity, the cytolysins, thrombase and cardiac toxin represent about 20 to 25 per cent and the proteolytic enzyme the balance But there are exceptions to this rule, as in *Crotalus terrificus* a viper, the venom is strongly neurotoxic

Minimal lethal doses of different venoms for man —Acton and Knowles (1921) estimated the minimal lethal dose (MLD) of cobra venom for man to be 15 mgm by a study of fatal cases of cobra bite given in the literature in which no treatment or valueless treatment had been administered The MLD for the venoms of other Indian species of poisonous snakes was also calculated by them on the assumption that the relative toxicities of different venoms for the monkey hold good for man

The data in the following table were taken from their papers and from other sources

TABLE XXXII

Snake	*Approximate dose given at bite mgm*	*Estimated fatal dose for man mgm*
Naia naia	211.3	15 0
Naia hannah	100 0	12 0
Bungarus candidus	5 4	1 0
B fasciatus	42 9	10 0
Daboia russellii	72 0	42.0
Echis carinatus	12.3	5 0
Trimeresurus gramineus	14 1	100 0
Agkistrodon makasen	45 – 60	approximately 25 0
A piscivorus	90 –150	
Crotalus horridus	60 – 90	
C adamanteus	240 –450	
Bothrops atrox	80 –160	
Lachesis muta	300 –500	
Dendraspis angusticeps (Mamba)	50 – 80	

SYMPTOMATOLOGY

As the toxic principles in colubrine and viperine venoms differ, the symptoms produced in the victim after the bites of the snakes of these two families are also different and they are therefore considered separately

Symptoms after colubrine (cobra) bite —Local Immediately after the bite there is a burning sensation at the site which passes off in a few minutes, this is followed by loss of sensation and paralysis of the area around the site, where a moderate amount of œdema supervenes There is oozing of blood from the fang punctures as the blood does not coagulate on account of the action of anticoagulin

General —The neurotoxins act on the motor end plates of muscles, on the respiratory centre and on the centres of the 9th 10th 11th and 12th nerves The following is the usual sequence of symptoms —drooping of the eyelids unsteady gait, incoordination of speech slight difficulty in respira
... down Paralysis starts from the lower
e except for the local paralysis
s upwards With the complete
paralysis of all the voluntary muscles there is drooping of the head and difficulty in deglutition Asphyxial symptoms supervene breathing becomes shallow and rapid, and the face becomes cyanotic There is profuse salivation Later convulsions start and there is vomiting and involuntary passage of urine and fæces Finally, the victim dies of respiratory failure The pulse is little affected except as a result of primary shock which is

mainly due to fright The heart continues to beat after the respiration has failed Consciousness is retained almost to the last Death usually takes place in untreated cases in from one to six hours

The symptoms after krait bite are similar to those of cobra bite with an additional symptom of violent abdominal pains which is associated with hæmorrhages in the stomach and the intestines

Authentic cases of sea snake bite are rare The symptoms caused by their bite are similar to those after cobra bite

Symptoms after viperine bite (Russell's viper) —Local Immediately after the bite there is an intense burning pain which persists along with the incessant oozing of blood from fang punctures There is also marked œdema and redness of the area and later ecchymoses around the puncture There is no loss of sensation or paralysis of the bitten part

General The hæmorrhagin destroys the endothelial cells of the finer capillaries and blood escapes through them In consequence there is evidence of external as well as internal hæmorrhages There may be epistaxis hæmaturia hæmoptysis hæmatemesis melæna sub-conjunctival [illegible]

supervenes in fatal case of viper bite Death usually takes place in two to six days

The above symptoms are produced if a moderate quantity of venom is injected If on the other hand a large amount is injected with the bite death occurs in a few hours as the result of acute cardiac and vasomotor failure or if by any chance the venom is introduced directly into a vein death follows within a few minutes as the result of intravascular and intra cardiac coagulation but this occurrence is very rare in human beings Whereas death after Russell's viper bite is usually due to vasomotor paralysis or to septic absorption from the extensive local gangrene in the case of *Echis* bite death is usually due to multiple hæmorrhages

The effect of the bite of the rattlesnake —The effect of the bite of the rattlesnake genus *Crotalus* is similar to that of the viper there is much pain local swelling and hæmorrhagic reaction The hæmorrhagic mottling and swelling tend to spread up the limb from the site of the bite Later general symptoms of viperine poisoning develop The exception to this rule is the bite of dog faced rattle snake (*Crotalus terrificus* whose venom is strongly neurotoxic and causes little local reaction but later the vision and respiratory centres are affected

DIAGNOSIS

The first important point to decide is whether the patient has been bitten at all [illegible] on poisonous [illegible] ce the snake [illegible] will seldom [illegible] fication possible On rare occasions the offender is caught and killed then it will usually be possible to decide on its identity (*see* p 846) Diagnosis will

therefore often depend largely on the local examination for marks and on the signs and symptoms presented by the patient But diagnosis is not easy, one cannot afford to await the development of typical symptoms or it will be too late to take any action

The part where the bite is supposed to have occurred should be examined carefully for the *teeth and/or fang marks* *The harmless* aglyphous and the relatively harmless opisthoglyphous snakes may leave the marks of two double rows of teeth, the posterior fang of the snakes of the latter group seldom coming into action when biting man, whereas the proteroglypha

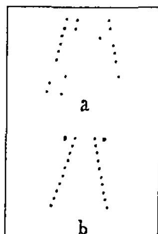


Figure 195 Showing upper-jaw fang marks of
(a) Aglyphous (non-poisonous) snake
(b) Proteroglyphous (poisonous) snake

glypha often leave only a pair of bleeding fang marks, as they 'strike' rather than 'bite' The larger the snake the greater the distance between the fang marks

Before considering the diagnostic points in the symptomatology of poisonous snake-bite, it will be as well to review the symptoms that are likely to occur after the bite of a non-poisonous snake

Non-poisonous snake-bite.—Fear of snake-bite is so highly developed in the human race that many people suffer from a severe degree of primary shock even after a bite by a non-poisonous snake In so-called strong-nerved —that is unimaginative—individuals, one might be able to discount the effects of fear, but it is no easy matter to gauge a person's

ys first
nptoms
audible
corded
irmless

snake In a person who is familiar with the symptoms of snake bite, all

result
rhages
whom

there will be only very

sligh d fang marks will be

abse ill be no bleeding from

them, also there will be no local ... nor paralysis, but these may be simulated by an hysterical patient

Differentiation between colubrine and viperine poisoning—This also is difficult in the early stages when the differentiation may be of any value In colubrine poisoning, local pain passes fairly rapidly and is replaced by local anæsthesia, *local paralysis develops, and there is some local* œdema In viperine poisoning, local pain is marked and persistent; there is a more intense local reaction which may include echymosis around the puncture,

and there will be no local paralysis In the later stages, more marked differences in the general symptoms appear (*vide supra*) Shortly, the predominant symptoms in the former are paralytic, and in the latter hæmorrhagic

PROGNOSIS

This is dependent on a large number of factors several of which are unappraisable, and it must therefore be very guarded (It is however essential that the patient himself must be reassured for his own sake)

The factors concerned are

(*a*) the species of the snake and the individual variation in the toxicity of its venom, (*b*) the amount of venom injected (*c*) the site of the bite, (*d*) the body-weight of the victim (*e*) the immediate measures adopted, and (*f*) the facilities available for treatment

(*a*) If the snake is not identified, this factor can only be gauged in general terms, for example the snakes of Europe Australia, and temperate countries generally are much less poisonous than those of India and other tropical countries

(*b*) The amount of venom injected is dependent on the efficacy of the bite which will to some extent depend on (*c*) the part bitten, a bite on a small member, such as a finger or toe, or even hand or foot is likely to be more effective as, for mechanical reasons the poisoning mechanism can come into full play, on the other hand, in such a position it will be easier to give effective local treatment

(*d*) The body weight is important, as the effect of a given amount of poison will be in inverse ratio to the body-weight, therefore the larger the individual the better are his chances of recovery

(*e*) The prompter the application of the ligatures and other immediate measures, the better the prognosis

(*f*) Finally, to be of any use specific or polyvalent serum must not only be immediately available, but available in sufficient amount

TREATMENT

Introduction —More fables have grown up around the treatment of snake bite than around any other procedure in medical practice Many millions of inhabitants of eastern countries are firm believers in amulets, snake stones potions with a most diverse range of ingredients—from plant juices to powdered gall stones—and/or prayers and incantations as infallible cures for snake-bite This credulity is not confined to the uneducated classes nor even to the inhabitants of eastern countries, for there is a widespread belief amongst the laity of western countries—a belief that is even accorded semi-official recognition in countries where 'prohibition' is in force—that the drinking of a bottle of whiskey is the best treat- [illegible]

bility

There is no specific treatment for snake bite other than the appropriate antivenom serum, although there are many non specific procedures,

that must be considered as adjuvants when antivenene is available and as substitutes when it is not

It will be suitable first to consider shortly these non-specific procedures, then the specific treatment, and finally the practical aspects of the treatment of snake-bite in various circumstances

Non-specific Procedures

(*a*) **Localization of the venom** —(i) **Tourniquet.**—The application of some form of tourniquet, either a tightly applied one to prevent arterial flow, or a lightly applied one to cause venous congestion and control lymph return, appears to be the common-sense procedure, but nevertheless it is not a measure that is universally recommended The main case against the tourniquet is that no tourniquet will prevent poison spreading through the tissues and an arterial tourniquet at least will often do considerable and unnecessary local damage On the other hand, most practical workers consider that a lightly-applied tourniquet is always beneficial and some recommend an arterial tourniquet as *well* The writers believe that combined with other measures at least a light ligature should be applied, and one of us (S K G) has seen marked benefit from an arterial ligature in preventing the neurotoxin reaching the central nervous system in colubrine bites

(ii) **Refrigeration** —There is little practical support for this theoretically plausible procedure, but it is sometimes worth practising if only for its psychological effect

(*b*) **Elimination of venom at the site** —(i) **Multiple incisions** should be made with aseptic precautions and if possible under local anæsthesia a large deep (¼ to ½ inch according to the depth of the bite) crucial incision through the fang marks and a series of small (¼ inch by ¼ inch) incisions around the edge of the advancing swelling, blood vessels must be avoided and, if cut, tied

(ii) **Suction** may be effected by means of Bier s suction tubes, a breast
that suggested by Jackson
e wound should be looked
be combined with ligature
and saline irrigation, and continued for a long time Although much of the toxin is absorbed by the local tissues, a considerable amount can be extracted by this means, as experience has shown that the extracted fluid is very toxic

(iii) The objects of **excision** and **amputation** are the same, namely, the removal of the tissues in which the toxin is fixed The choice of procedure will depend on the site of the bite, and amputation should only be [illegible] on the toes or fingers These measures should

(*c*) **Neutralization of the venom** ***in situ*** —Local infiltration with calcium hypochlorite, potassium permanganate, gold chloride or other substances, some of a secret nature, has been advocated in the past and is still considered by some workers to be a valuable procedure However, the present trend of opinion is against any local injection, except with antivenene The latter, if available, should always be used, at least in the case

of viper bite and as much as they will take should be infiltrated into the tissues around the bite

(*d*) **Treatment of general symptoms** —(i) **Primary shock** —The pa ead slightly lower than his feet reassured and calmed Caffeine ¼ grain, if there is severe pain bvious that the bite was a non poisonous one in such a case given in moderate amounts it will help to combat primary shock from fear

(ii) **Secondary shock and collapse** —Hæmorrhages and vasomotor failure may lead to collapse which should be combated by the usual pro cedures including plasma or serum transfusions of at least two pints and pituitrin and adrenalin In the absence of plasma whole blood may be used Chopra and Chowhan (1939) strongly advocate veritol (15 30 mg intramuscularly or 40 80 mg by mouth)

[illegible]

(iv) **Respiratory paralysis,** caused by the neurotoxins may occur Respiratory stimulants such as coramine and cardiazol by the parenteral route may help to alleviate respiratory embarrassment but in some cases artificial respiration and oxygen may have to be maintained for several hours

(*e*) **Treatment of complications and sequelæ** —(i) **Sepsis** —Septic ab sorption from the site after viperine bite is not uncommon Early adminis tration of drugs of the sulphonamide group prevent this complication Some authorities advocate the routine use of antitetanic serum in prophy lactic doses

(ii) **Gangrene** —It frequently occurs after viperine bite and is due to the action of thrombase Early administration of antivenene early release of the ligatures and when the general symptoms appear to be well con trolled vigorous local treatment with frequent hot fomentations will usually prevent gangrene but once it supervenes amputation is the only remedy

(iii) **Other complications and sequelæ** —*Hæmopericardium hæmo thorax hæmarthrosis pyæmia* and *nephritis* are some of the sequelæ of viperine bite each of these requires its own line of treatment

SPECIFIC TREATMENT

Antivenene —The only specific treatment against poisonous snake bites is the early administration by the intravenous route of antivenom serum so called antivenene As the venoms of different species of snakes differ in their toxic principles different antibodies are produced in the im munized animal (horse) and the antiserum produced against the venom of a particular species is effective against that venom alone or against the venom of closely related species For example in India antivenene either against cobra venom or Russell s viper venom (the two commonest poison ous species which are responsible for the majority of the 20 000 or more annual snake bite deaths) will not protect the victim bitten by the other species To surmount this difficulty polyvalent sera which are effective against more than one common local species have been prepared by serum

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(*iii*) The objects of **excision** and **amputation** are the same namely, *the removal of the tissues in which the toxin is fixed* The choice of procedure will depend on the site of the bite and amputation should only be considered in the case of bites on the toes or fingers These measures should only be undertaken when the limb has been effectively ligatured continuously *since the bite*, or when it is possible to excise the site or amputate the limb immediately after the bite

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(iii) **Hæmorrhages** —For the multiple hæmorrhages after viperine bite, injections of calcium chloride or gluconate, congo red solution, vitamin C, vitamin K and hæmostatic serum have all been advocated and each appears to have been of value in certain cases

(iv) ***Respiratory* paralysis**, caused by the neurotoxins, may occur Respiratory stimulants such as coramine, and cardiazol by the parenteral route may help to alleviate respiratory embarrassment but in some cases artificial respiration and oxygen may have to be maintained for several hours

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institutes of different countries * Heterologous serum is sometimes used but there is little evidence that it is of any real value

Dosage.—The points to be considered in calculating antivenene dosage are —

(*a*) The amount of venom inoculated, this is an unknown quantity, but the average quantity injected by a snake of the particular species is usually known (*see* table XXXII, p 850), and some idea of the efficacy of the bite may be obtained from the site and the circumstances of the bite

(*b*) The toxic activity of the venom of the individual snake, this is always an unknown quantity, but is likely to vary from country to country and the venom is usually more toxic in tropical countries

(*c*) The neutralizing capacity of the antivenene, for example, whether it is concentrated or not; 1 c cm of polyvalent antivenene (Kasauli) given intravenously will neutralize 0 4 mgm of dried cobra venom or 0 9 mgm of daboia venom

(*d*) The time that has elapsed after the bite

(*e*) The route of administration, the intravenous route is three to four times more effective than the intramuscular or subcutaneous

It will be seen from the above and from table XXXII on p 850 that the amount of concentrated polyvalent antivenene, for intravenous in-

should be remembered that such large doses of horse serum by the in-

---

* In India, the Central Research Institute, Kasauli (Punjab) prepares and issues ... enene which is effective ... oncentrated four times ... 40 c cm of unconcen- ... of the Institute at a cost of about four rupees per ampoule

Polyvalent high titre antivenene against two or more different local species are being produced by —

(*a*) Butantan Institute in Sao Paulo, Brazil South America prepares four polyvalent antivenenes against (i) rattlesnakes (ii) Bothrops (iii) rattlesnakes and Bothrops, and (iv) coral snakes

venene against the ...

(*e*) Public Health Department of New South Wales, Australia prepares an ...

repare a 'nearctic cratolidæ' ... ipers) and a Bothrops anti- ...

) c cm of serum which have ... It is probable that the ... to a powder will be applied ... essity of keeping them in a

travenous route may cause severe anaphylactic symptoms in susceptible individuals

Precautions—In the case of persons giving a history of allergy, such as asthma or hay fever, or of previous injection of horse serum a test for sensitiveness to the proteins of horse serum must be made by giving intradermally 0 1 c cm of a 1-in-10 dilution of horse serum If no skin reaction

the patient before giving the main dose

way in 0 1 the oms

occur, the injection should at once be stopped and 1/50th gr of atropin and 0 5 c cm of a 1 in 1 000 solution of adrenalin chloride should be administered hypodermically

We have usually adopted the practice of giving 50 c cm of concentrated antivenene intravenously diluted with the same quantity of 25 per cent glucose solution to start with and then the balance of the dose slowly in a pint of 5 per cent glucose in normal saline No ill-effects were noticed in any of the patients

After the requisite quantity of antivenene has been given the ligatures may be removed

PRACTICAL CONSIDERATIONS

When ... the first problems facing the prac ... te patient was actually bitten at ... poisonous one and in the former ... dangerous dose He then has to decide how far he is justified in carrying out possibly mutilating procedures on the chance that the snake may have been a poisonous one and that the dose may have been one that would ordinarily prove fatal

If the snake is captured or killed and is not too badly mutilated it ... for tooth and/or ... the surrounding

Prompt action is ne ... be weighed on the evide ... naturally be somewhat ... ment is to be given for ... poisonous it would be wrong to withhold antivenene ... would hesitate to take such drastic procedures as amputating a limb or even making extensive incisions which might damage important structures and would usually be a potential source of sepsis unless the suspicion were well founded

It will be as well now to consider the case of snake bite as an emergency in four different sets of circumstances

A In the jungle or bush where no medical equipment is available and first aid has to be applied

B In the isolated village dispensary where no antivenene is obtainable

C In an out-station hospital where, although there is no antivenene at hand this will be obtainable within a few hours

D In a well-equipped hospital where antivenene is available in sufficient quantity

A In the jungle or bush where no medical equipment is available, and 'first aid' has to be applied—A ligature must be placed immediately

suction should be applied over the punctures and, if a sharp and reasonably clean knife is available, a crucial incision may be made into the fang marks to facilitate effective suction, but it is doubtful if any further cutting procedures should be undertaken in these circumstances The patient must be reassured as far as possible and, when they are available, given hot coffee or tea to drink and ¼ grain of morphia subcutaneously He must then be removed to the nearest place where further treatment can be given

Wherever possible the snake should be killed, without damaging the head unduly, and identified or preserved for identification

Do not give alcohol if it is thought that the bite was by a poisonous snake, as it is definitely detrimental

B In the isolated village dispensary where no antivenene is obtainable—This is the situation that probably nine times out of ten faces the medical man who has to treat snake bite in tropical countries A firm ligature sufficient to stop the lymph flow and the venous return should be

—ven (*vide supra*) The patient
closely regarding the incident
s of the snake having been a
poisonous one This will be facilitated if the snake was killed and brought with the patient If the decision is in favour of an effective bite by a poisonous snake, then under a local or a general anæsthetic a series of incisions should be made under strict antiseptic conditions, one deep crucial incision immediately over the bite, a number of shallower (¼ inch) crucial incisions in a circle around the bite at the edge of the swelling and, if the swollen area is a wide one several incisions should be made within this

and any symptoms that have developed

Other treatment for secondary shock and other general symptoms, and for the various complications that may arise will naturally be given (*vide supra*)

antivenene is obtained Primary shock must be treated, and other symptomatic treatment applies as necessity arises

D. In a well-equipped hospital where antivenene is available in sufficient quantity.—If no tourniquet has been applied, both tourniquets and ice should be
being questione
injection Prim
given, intravenc
If there is any
than genus-spec
krait bite when
available—local treatment for eliminating the venom must be undertaken (*vide supra*)

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RABIES

Definition—Rabies or hydrophobia is a zootic disease which is potentially world wide in its distribution but has been excluded from certain countries and entirely banished from others it is however always a serious problem in the tropics It is caused by a filtrable virus which is transmitted to man by the bite of carnivores usually canines The virus spreads along the nerves and the symptoms are mainly of a nervous nature excitation and/or depression and later paralysis When the symptoms are established the disease is invariably fatal

EPIDEMIOLOGY

One of the reasons for the relatively heavy incidence of rabies in the tropics is the presence of innumerable stray dogs and of other actual and potential reservoirs of infection for example jackals foxes and mongoose in India and vampire bats in Brazil Trinidad and Jamaica Another cause is general administrative and sanitary backwardness in these countries

The disease is very widespread in India and in the Pasteur Institute in Calcutta which is only one of several such institutes in the country as many as 10 000 persons undergo anti rabic treatment' annually It is also very prevalent in Africa and South and Central America

The disease has apparently never been introduced into Australia this is the result of rigid quarantine rules aided possibly by the absence of any

potential wild reservoirs of infection It was banished from Great Brita by rigidly enforced muzzling orders of half a century ago as well as by t adoption of a six months quarantine period for imported dogs but w temporarily reintroduced after the First World War apparently by returning soldiers dogs which evaded the quarantine regulations In United States where the control problem is admittedly a complex one account of its many miles of land frontier between fifty and sixty dea from rabies occur each year

There is a popular superstition that the disease is confined to cert seasons of the year especially the late summer days There is no statisti support for this belief

ÆTIOLOGY

The causal organism is a medium sized filtrable virus about 125 mi microns in diameter For infection to occur the virus must reach ne tissue, it cannot therefore be transmitted through the unbroken skin mucous membrane

By repeated sub passage of the virus directly on to the brain of series of rabbits or sheep it is possible to change an ordinary stre virus with its long and inconstant incubation period into a virus with fixed incubation period of three to six days After attenuation—by one several recognized methods—this fixed virus introduced subcutaneou into man is usually innocuous but retains its antigenic properties

Most animals are susceptible to infection but not all are capable true of the large herbiv As far as man is concern ts are the only import may act as regional res ng 1941 out of 7 877 ca of rabies 6 648 were in dogs The dog may have the virus in its saliva 3 4 days before symptoms of the disease appear and it remains infectio until it dies death usually occurring within six days of the onset symptoms

PATHOGENESIS

The virus spreads up the nerve trunks until it reaches the cord fr

tem lays ie c

The most characteristic specific changes are produced in the pyramid cells of the hippocampus major where the specific Negri bodies are m readily found though they are often present in other nerve cells in t brain Negri bodies are acidophilic bodies observed in the cytoplasm the nerve ganglion cell, they vary considerably in size and shape usua being 3 to 10 microns in diameter and round or oval in shape and granular in appearance Negri bodies are not parasitic structures but res from the reaction of the cell to the virus and are comparable to the clusion bodies that are seen in various parenchyma cells in other vi infections

SYMPTOMATOLOGY

The incubation *period is from two weeks to six months*, this is influenced by several factors, including the site of the bite (*vide supra*) The onset is usually preceded by a day or so of malaise, headache, insomnia, irritability, and slight fever, or the onset may be sudden, with the development of periods of restlessness, anxiety and hyperexcitability Breathing becomes rapid and 'air-hunger' may develop These periods of excitement alternate with periods of calm, but the former tend to become longer and soon are accompanied by actual spasms of muscle groups, such as those of deglutition These spasms are precipitated when the patient attempts to drink, and in his thirsty state even the sight or thought of water may cause the spasmodic retraction of the head in a series of jerks Spasms are also precipit
ment
patient'
Later, t
but eve
and the mouth is often filled with a ropey and frothy mucus There is often a low fever

Eventually, the patient sinks into a paralysed and weak state and death follows, or this may occur suddenly during one of the spasms, within 2 to 3 days of the onset of symptoms

Other types have been described, including a form in which paralysis develops from the onset and simulates acute ascending myelitis

DIAGNOSIS

The combination of the history and clinical picture are usually sufficient to make a diagnosis certain, but hysteria, malingering, tetanus, meningitis, encephalitis and poisoning and, in the paralytic type, other paralyses, *e g* Landry's, may have to be excluded

Post-mortem diagnosis may be made in man or dog by examination [illegible] Both impression and crushed
f the
d by

Cerebral inoculations of mice should also be made Webster (1942) recommends the following procedure:—

'A [illegible] of the suspected animal is emulsified by grinding it
in a mc and *injected in*
0.03 cc 2 to 3-weeks-old
d for

If the suspected material really contains rabies virus the mice usually [illegible] Negri bodies *on the 5th or 6th* days, become sick on the 7th to 10th days, and die on the 9th to 12th days They are generally uniform in their response—either nearly all become sick and die or all remain well Rarely do the mice remain well for periods of 15 days and then develop rabies'

Great care should be taken to avoid self infection while carrying out these examinations

Whenever possible expert advice should be obtained and if examination is to be carried out elsewhere the whole brain in the case of man and the whole head in the case of the dog should be sent in a suitable receptacle to the laboratory on ice—not on dry ice

PREVENTION

Control of rabies in animals —This is first a matter of wise legislation and then rigid enforcement of the laws made Six months quarantine for imported dogs the licensing of all dogs and the destruction of all stray (unlicensed) dogs and the muzzling of all dogs while at large or in any public place whenever there is a rabies epizootic have successfully controlled this disease in several countries Compulsory inoculation of dogs has also been adopted with success It may be necessary to maintain these control measures over long periods and some of them of course permanently especially when there is a danger of reintroduction of infection by wild carnivores but rabies is an essentially controllable disease and should be controlled

Control of the infection in man —When an individual is bitten by a dog that is known or suspected to be rabid the wound should be cleaned immediately and **cauterized** After protecting the skin with vaseline this may be done carefully with fuming nitric acid or pure phenol which should be washed out with sterile saline powdered potassium permanganate can also be used The extent of the cauterization must depend on the site of the bite and on the chance of the dog s being rabid While it must be admitted that unsightly scars have often been produced unnecessarily there is considerable evidence that skillful cauterization is of value Cauterization must not be used as an excuse for neglecting anti rabic vaccination

Anti rabic vaccination should be carried out as early as possible in every case of effective bite by a dog which is known to be rabid Before this step is taken a determined effort to find out whether or not the animal was rabid should be made When it can be caught it should be shut up and kept under observation and if it dies within 10 days or shows obvious signs of rabies and has to be destroyed the brain must be examined or sent for examination for evidence of rabies if it survives this period it may be assumed that it was not rabid

The rabid animal —The first evidence is a departure from normal behaviour and disposition An unusual display of affection or the reverse a withdrawal from human and canine company irritability and snappishness should arouse suspicion Later the animal will often run *amok* biting

Many febrile conditions such as distemper will cause cerebral symptoms especially in the young dog these symptoms may include irrational behaviour with apparent aural and visual hallucinations which will often simulate rabies

The virus is present in the salivary glands of a dog 3 to 4 days before it shows evidence of rabies

Indications for vaccination —Whether anti rabic vaccination is begun immediately or whether a report on the dog is awaited will depend on circumstances the probability of the dogs being rabid and on the nature and location of the bite In the case of severe bites on the upper limb and face treatment should be begun immediately if there was any possibility that the animal was rabid the same applies to any effective bite if there is strong evidence that the animal was rabid On the other hand if the animal is under observation and the bite is a slight one through clothes or on the trunk or lower limbs it will be safe to await the verdict on the condition of the dog Further when a dog under observation is declared non rabid any course of treatment commenced can be discontinued

The virus does not enter through the unbroken skin so that licks and other contact with rabid animals are not an indication for anti rabic vaccination It is however, the practice in most Pasteur institutes in India

Anti rabic vaccination —Many types of vaccine both dead and alive have been used There is considerable evidence that the best and most economical to prepare on a large scale is phenolized sheep vaccine made up as a 1 per cent emulsion of sheeps brain It is given subcutaneously in doses of 5 c cm daily for 14 days During the course of injections the patient is advised to take only light exercise and to avoid alcohol

The only post vaccinal accident other than the avoidable ones due to sepsis is paralysis varying from that of a localized group of muscles to an ascending paralysis of the Landry type This sequel only occurs in about one in ten thousand cases when killed vaccine is used although more frequently with live vaccine The difference suggests that many of the latter cases are examples of fixed virus rabies It is very rarely fatal

TREATMENT

No specific treatment of the slightest value has yet been discovered

The patient should be put to bed in a darkened room protected from all external stimuli and kept under the influence of sedatives and anti spasmodics of the latter the classical one is atropin Sedatives must be administered in particularly large doses if they are to produce their effect

PROGNOSIS

Experience indicates that once symptoms have developed the infection cannot be overcome and a fatal issue is inevitable It must however be appreciated that there are many factors namely the position* and depth of the bite the genus of the biter (jackal bites are more frequently fatal

*The importance of this factor is well brought out in a recent report of the Pasteur Institute of Bengal attached to the Calcutta School of Tropical Medicine an analysis of the Indian patients who underwent treatment during 1939 shows the following —

Position of Bite	Number Treated	Deaths	Death Rate
Leg	3,203	12	0.375
Trunk	164	0	—
Arm	1,877	16	0.85
Head	250	11	4.40

than dog bites), the interposition of clothing, and the infectivity of th bite, to be taken into account, and it has been diversely estimated by differ ent observers that from 2 to 80 per cent of all persons actually bitten b rabid animals, if untreated, would develop the disease The present da opinion is that the figure is about 10 per cent, and that efficient anti-rab treatment will reduce the death rate in these persons, as a group, to abou 2 per cent, but here yet another variable factor comes in, the time after th bite at which treatment is given Most Pasteur institutes give a low death rate than this, but their figures are usually diluted by a large numbe of persons who were not bitten at all or who were bitten by non-rabi animals

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A NOTE ON MYIASIS AND SCARABIASIS*

MYIASIS

At times, invasion of the tissues and organs of man and other animals by fly maggots may take place This condition is comprehensively known as myiasis

The screw-worm larvæ of *Chrysomyia bezziana* will infest the natural orifices of the human body, such as the ear, mouth, eye, nose, and vagina and cause considerable destruction of tissues Myiasis due to *Cochliomyia hominivorax* is common in man in tropical America

The flesh-fly, *Sarcophaga*, generally causes external myiasis The larvæ are deposited on gangrenous sores, lacerated wounds, etc and being saprophagous in their habits they bring about a rapid healing of the ulcers Larvæ of *Sarcophaga sp*, and
cessfully employed in the trea
whereas in America larvæ of
phora erythrocephala grown n
artificial maggot therapy

Cutaneous myiasis is often caused by larvæ of bot-flies, subcutaneous tumours are generally produced The maggots of sheep bot-flies *Œstrus ovis* have been found in the conjunctiva and nasal cavities of man in the Central Sahara in the United States and elsewhere

Intestinal myiasis is to a great extent accidental, the larvæ being swallowed with food The frequency with which 'rat-tailed' larvæ of the drone fly, *Eristalis tenax*, occur in liquid excrement should make one extremely cautious in accepting the numerous reports of these larvæ being evacuated with the stools There are, however, several cases on record in which untoward symptoms such as indigestion, constipation emaciation and dysentery could be associated with these larvæ in the intestine

SCARABIASIS

the invasion of the intestine
by d ildren It has not been re-
port *Only those who have cut*
their teeth and are able to ... affected

The reports usually state that the insects are passed with the fæces at
... some months The passing of the beetles
ptoms of failing health such as loss of
dysentery, progressive emaciation and
temperature The stool is usually semi-

*By Dr D N Roy M D Professor of Entomology Calcutta School of Tropical Medicine

solid never hard, and after it has been voided, the attention of the mo is attracted to some movement in it a beetle gradually works it way u the surface, emerges and flies away As a rule the infestation is by n than one beetle and sometimes over a period of months large numbers passed the health of the child improving in the intervals Strickland Roy (1939) have discussed at length the method by which these ins gain access to the alimentary canal and they believe that the infesta takes place *per anum*

Instances have been reported from the eastern parts of India Ceylon also from South Africa

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SUBJECT INDEX

Caps and small caps indicate chapter title and sub-title

AUTHOR INDEX

Page numbers which appear in italics indicate that a full reference appears at the end of the chapter in which the author's name occurs